Cancer Treatment Reports

A Publication of the National Cancer Institute

Volume 70
Number 12
December 1986

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES Public Health Service National Institutes of Health

Cancer Treatment Reports

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9. The methods of statistical analysis should be described in detail sufficient that a knowledgeable reader could reproduce the analysis if the data were available.

**From* Methodologic Guidelines for Reports of Clinical Trials (Cancer Treat Rep 69:1-3, 1985).

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EDITORIAL

Interferons: Not Just Alpha[1]

Susan E. Krown[2,*]

Until now, alpha interferons (IFN-α) have dominated the center stage of IFN clinical investigations. They were the first, and the easiest, to be induced in large quantities and to be partially purified from human cells, and although not the first to be cloned and expressed in bacteria [interferon-beta (IFN-β) has that distinction (1)], they were the first human proteins produced by recombinant DNA techniques to be tested in large-scale clinical trials unencumbered by limitations of supply or by the ambiguities inherent in interpreting the results of trials with partially pure products of human cells contaminated with non-IFN proteins. Five years of clinical trials with recombinant IFN-α2 (rIFN-α2)[3], one of the more than a dozen distinct IFN-α species, have recently culminated in approval by the Food and Drug Administration for use in hairy cell leukemia—a highly IFN-responsive tumor—and it is likely that other approved indications will be forthcoming. Although many questions remain to be answered concerning the role of IFN-α in the treatment of cancer, it seems almost certain that they have secured a place for themselves in the repertoire of cancer therapeutic agents. For most physicians not intimately involved in this area of investigation, "interferon" has become synonymous with "interferon-alpha."

Two trials reported in this issue of *Cancer Treatment Reports*—one by Sarna et al (2) describing a phase I trial of serine-substituted rIFN-β, and the other by Kurzrock et al (3) describing phase I studies of recombinant IFN-gamma (rIFN-γ)—are timely reminders that the alpha IFNs are simply part of a larger family of proteins. As in any family, the members of the IFN family share many characteristics: all are capable of inducing a state of viral resistance in treated cells (the basis for the IFN bioassay); all can induce changes in the function of certain immune effector cells; all can inhibit the rate of cell growth in vitro; and, as detailed in the two trials reported in this issue, all are capable of inducing a characteristic range of qualitatively similar side effects. It is appropriate in these early trials of rIFN-β and rIFN-gamma to document toxicity, to define tolerated doses and treatment regimens, and to seek comparisons with the best studied member of the family, IFN-α. It may also be appropriate, as these less well studied IFNs are developed, to first determine their activity against tumors already known to respond to IFN-α. It was certainly not inadvertent that almost two-thirds of the patients in these phase I trials had tumor types reportedly responsive to IFN-α, and the glimmers of therapeutic activity detected were, indeed, observed primarily in patients with IFN-α-responsive tumors.

With IFN-α so far ahead in its clinical development, why now begin the same process with IFNs β and γ, if only to determine if they share the same therapeutic spectrum? This is, fortunately, a rhetorical question, for in seeking reasons to study the full range of IFN species we need only to recognize the diversity of members of the IFN family. Despite all their familial similarities, biological differences of potential therapeutic significance have been demonstrated between the three major antigenic types of IFN and even between the various IFN-α subtypes. Although the relative importance of direct antiproliferative activity versus indirect, host-mediated effects in inducing tumor regression is a complicated and, as yet, unresolved issue, it is certainly noteworthy that both IFNs β and γ have been superior to IFN-α in inhibiting the growth of certain tumor cell lines in vitro (4-6). It must be recognized, however, that these comparative studies were performed with only partially purified human or murine IFNs, and the presence of residual impurities and potential contamination

[1] Received Aug 22, 1986; accepted Sept 2, 1986.

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[3] The two approved IFNs, designated as IFN-α2a and IFN-α2b according to recent World Health Organization nomenclature guidelines, differ in a single amino acid at position 23. IFN-α2a (Roferon-A, Hoffmann-La Roche, Inc) was formerly called recombinant leukocyte A IFN (rIFN-αA; IFLrA); IFN-α2b (Intron-A, Schering-Plough, Inc) was formerly referred to as IFN-α2. Other IFN-α subtypes show 15%–25% variation in amino acid sequence.

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with other antiproliferative cytokines confounds interpretation of the results. Differences in tissue specificities have also been suggested for IFNs α and β, with IFN-α apparently having preferential effects on the growth of hematopoietic cells and IFN-β having greater antiproliferative effects on cells of nonhematopoietic origin (reviewed in ref 7). However, recent evidence supports a role for endogenously produced IFN-β as an autocrine growth factor during terminal differentiation of normal myeloid precursor cells, and during the induced differentiation of neoplastic myeloid cell lines (8).

The unique effects of IFN-γ on the expression of certain cell surface antigens and on the function and differentiation of cells of the B-cell and macrophage lineages have also suggested particular therapeutic applications. Although all IFNs can increase the expression of Class I histocompatibility antigens and β2 microglobulin, IFN-γ is a singularly potent inducer of Class II (HLA-DR) antigens on cultured tumor lines (9), normal macrophages (10), epithelial cells (11), and myeloid leukemic cells (12). The increase in HLA-DR expression on tumor cells and accessory cells may allow for more effective antigen presentation. In addition, we have recently reported that rIFN-γ treatment of a patient with chronic myelocytic leukemia was associated with increased HLA-DR expression on bone marrow granulocyte/monocyte colony-forming cells (CFU-GM), and the acquisition of sensitivity to prostaglandin E and acidic isoferritin, which act as negative regulatory factors in cultures of normal bone marrow (13). The ability of IFN-γ to induce phenotypic differentiation of neoplasms of early B-cell lineage in vitro (14) has also been confirmed in several of our patients treated with rIFN-γ (13,15). Chronic myelocytic leukemia and some of the B-cell lymphomas are also responsive to IFN-α, which lacks these differentiation effects in vitro, and it is conceivable that combined treatments might lead to more effective or durable control of these neoplasms. Synergistic antiproliferative effects of IFN-γ in combination with IFN α or β have, indeed, been well documented (16), as have synergistic interactions between various IFN species and other cancer treatment modalities (reviewed in ref 17).

The unique ability of IFN-γ to increase the oxidative metabolism of human macrophages, already demonstrated in cancer patients (13,15,18), has recently been confirmed in patients with lepromatous leprosy (19), a disease characterized by inadequate macrophage activation and deficient production of IFN-γ. In vitro, IFN-γ acts synergistically with other agents to promote macrophage secretion of tumor necrosis factor (20), a monokine that shows synergistic antitumor cytotoxicity when combined with IFN-α or IFN-γ (21). The increase in serum triglycerides and very low density lipoprotein observed in patients treated with rIFN-γ (3,15), also described in animal models and attributed to tumor necrosis factor (22), may well signify an indirect effect mediated via products of activated macrophages.

Armed with a substantial knowledge of IFN-α, and with a growing body of knowledge regarding the tolerance and pharmacology of IFNs β and γ, we can now begin to investigate the special role that each of these agents has to play in the treatment of cancer and other diseases. In approaching this task, it would be wise to remember the words of John Locke, who reminds us that "nature never makes excellent things for mean or no uses," and to fully explore the unique potential of each member of this diverse and excellent family of human proteins.

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Phase I Study of Iv Administered Recombinant Gamma Interferon in Cancer Patients[1,2]

Razelle Kurzrock,[3,*] Jorge R. Quesada,[3] Michael G. Rosenblum,[3] Stephen A. Sherwin, [4] and Jordan U. Gutterman[3,5]

We report a phase I study of the biological effects, tolerance, and pharmacokinetics of 6- and 24-hour iv infusions of recombinant interferon-gamma (rIFN-gamma) in cancer patients. Twenty-one patients received the 6-hour iv infusion regimen at doses ranging from 0.016 to 0.65 mg/m^2/day. Forty-one patients received the 24-hour iv infusion regimen at doses ranging from 0.01 to 0.05 mg/m^2/day. Fever and flu-like symptoms were the most common side effects and were seen at all dose levels. The maximum tolerated dose was 0.16 mg/m^2 for the 6-hour regimen and 0.01 mg/m^2/day for the 24-hour regimen. A dose-dependent granulocytopenia was observed at doses $\geq$ 0.05 mg/m^2/day. A marked increase in beta$_2$ microglobulin occurred by Day 5 of treatment in almost all patients, regardless of the dose level. Consistent serum levels of rIFN-gamma were achieved only at doses of 0.325 mg/m^2/day of the 6-hour infusion. The mean serum concentrations at this dose ranged from 18 to 83 units/ml as measured by bioassay (0.64–2.4 ng/ml by enzyme-linked immunoassay). Antibody against rIFN-gamma did not develop in any patient. During the short period of evaluation of this study, one patient with renal cell carcinoma achieved a partial response, and three patients with renal cell (two) and lung carcinoma (one), respectively, achieved minor responses. This study will form the framework for phase II efficacy trials of iv rIFN-gamma. [Cancer Treat Rep 70:1357–1364, 1986]

Since the initial discovery of the interferons by Isaacs and Lindenmann (1) in 1957, potent antiviral, antiproliferative, and immunoregulatory activities have been identified for these proteins (2,3). These properties have stimulated interest in the evaluation of potential salutary effects of the interferons in a wide range of human illnesses, including cancer, infectious diseases, and immunocompromised states.

Clinical studies indicate that interferon-alpha (IFN-alpha) is active in man against both viral diseases and certain types of malignancies, including hairy cell leukemia, chronic myelogenous leukemia, Kaposi's sarcoma, lymphoma, and renal cell carcinoma (4–10). Interferon-gamma (IFN-gamma) is a structurally distinct interferon which is derived primarily from T cells (2). Although IFN-gamma shares many functional properties with IFN-alpha, there are important differences in the biological spectrum of action of these molecules that may eventually prove clinically useful. Recent in vitro studies have suggested differential sensitivity of target cell lines to the antiproliferative effects of IFN-gamma versus IFN-alpha (11). IFN-gamma is a more potent immunoregulator than IFN-alpha, particularly of tumoricidal and microbicidal macrophage activity (12). In addition, this agent is unique in its ability to differentiate both normal and tumor B-lymphocytes as well as myelomonocytic cells in vitro (13–15). This latter property may be exploitable in overcoming the maturation block characteristic of many human leukemias and lymphomas.

Recently, synthesis of IFN-gamma in *Escherichia coli* by recombinant DNA techniques has allowed production of large quantities of highly purified material (16) suitable for clinical investigations. Our pharmacokinetic studies of recombinant IFN-gamma (rIFN-gamma) revealed that this agent had a rapid serum disappearance

[1] Received Mar 31, 1986; revised July 15, 1986; accepted Aug 4, 1986.

[2] Supported by a grant from Genentech, Inc. and the John D. and Katherine T. MacArthur Foundation. Research conducted, in part, by the Clayton Foundation for Research and the James E. Lyon Foundation. J. Gutterman is a Senior Clayton Foundation Investigator.

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[5] We thank the nursing staff, Donnah Jones, Margaret Harle, Paula DeAvries, and Andrea Linder, for their assistance. We also thank our physician assistant, Mary Jo Hemmer, and data manager, Brigitta Burgess, for their help in conducting the studies and in the preparation of this manuscript.

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with a half-life of approximately one-half hour after iv bolus injection (17). Previous in vitro work has demonstrated that activation of cells by IFN-gamma requires many hours of incubation with this agent (18). These data suggest that iv administration of rIFN-gamma should be given over several hours in order to allow for the prolonged exposure to this molecule which may be necessary for eliciting optimal biological effects, including antitumor activity. Therefore, we initiated a phase I study whose objectives were to investigate the biological properties, tolerance, and pharmacokinetics of prolonged iv infusions of rIFN-gamma in cancer patients.

MATERIALS AND METHODS

Patient Selection

Patients with histopathological verification of metastatic cancer were entered on the study. Eligibility criteria included the following: a Karnofsky performance status $\geq$ 50% (19); no anticancer treatment for at least 3 weeks before initiation of interferon; a life expectancy of at least 3 months; and preserved hepatic (bilirubin $\leq$ 1.5 mg/dl), renal (creatinine $\leq$ 2 mg/dl), and hematological functions (granulocyte count $\geq$ 1500/mm^3 and platelet count $\geq$ 100,000/mm^3). Patients requiring ongoing therapy with corticosteroids or nonsteroidal antiinflammatory drugs were excluded from the study. Informed consent was obtained from all patients according to institutional policy.

Study Design

Patients on study were monitored daily. Vital signs, including heart rate, blood pressure, temperature, and respiratory rate, were recorded before injection and at 2, 4, and 6 hours after the start of the infusion. A physical examination was done before the initial dose and weekly thereafter while the patient was on the study. A cbc was performed daily on Days 1–8 and weekly thereafter. Electrolytes, urinalysis, prothrombin time, partial thromboplastin time, reticulocyte count, and a chemistry profile including renal and liver function tests were obtained before treatment and then twice weekly. Triglycerides and cholesterol were measured weekly, after an overnight fast. An ECG and chest roentgenogram were done before the study and after the final dose. Evaluation of tumor size was done by physical examination and appropriate radiological studies and scans as well as tumor markers. The criteria for responses have been previously described (10).

Symptoms were classified as "mild," "moderate," or "severe." "Mild" referred to symptoms that caused no change in performance levels and did not require medication for relief. "Moderate" referred to symptoms that required medication for relief. "Severe" signified symptoms that were inadequately relieved by medication and caused a > 25% drop in performance status. Fevers were considered severe if they persisted at > 39°C for > 6 hours per day, in spite of acetaminophen therapy. Chills were labeled severe if they were present for > 3 hours per day. Changes in laboratory parameters were also classified according to their degree of abnormality. Changes in laboratory values designated "severe" included the following: granulocyte count < 750/mm^3, platelet count < 50,000/mm^3, bilirubin > 2.5 mg/dl, SGOT > 300 IU, or creatinine > 3.0 mg/dl.

The study included 6- and 24-hour iv infusion regimens. Patients were entered sequentially onto the 6-hour iv infusion arm until the maximum tolerated dose was reached. This arm of the study was then closed and patients were entered sequentially onto the 24-hour iv infusion arm until the maximum tolerated dose of this regimen was reached. On the 6-hour iv infusion regimen, there were at least two patients entered at each dose level starting with the lowest level (table 1). Patients were given a 5-minute bolus iv loading dose of rIFN-gamma followed by a 6-hour iv infusion, daily for 10 days. Doses were selected based on our previous experience with single iv bolus doses of rIFN-gamma (17). Following a rest period of at least 7 days, patients were restarted on a repeat 10-day cycle of rIFN-gamma. The dose level at which patients were restarted depended on the degree of toxicity during the previous cycle. Patients who experienced only "mild" toxicity during the first 10-day cycle were restarted at the next highest dose level during the second cycle, while patients who experienced "moderate" toxicity received the same dose of rIFN-gamma during the second cycle. Patients who experienced "severe" toxicity had the dose reduced to the next lower dose level. If "severe" toxicity recurred, interferon was discontinued. After every 27 days on study (two 10-day cycles of therapy with an intervening 7-day rest period), tumor size was evaluated. Interferon therapy was discontinued in those patients who showed no response or progressive disease. Patients who showed evidence of response were continued on either escalating doses or the same dose, depending on their previous toxicity, as outlined above.

In the second arm of the study, each patient received a fixed dose of rIFN-gamma by 24-hour continuous iv infusion for 28 days. Patients were entered sequentially onto each of the dose levels, as outlined in table 1. Treatment was withheld from any patient with toxicity

TABLE 1.—Treatment plan

Dose level	Bolus dose (mg/m^2)	Infusion dose (mg/m^2/hr)	Total dose mg/m^2/day (U/m^2/day)
		Schedule 1: 6-hr iv infusion	
1	0.001	0.0025	0.016 (0.32×10^6)
2	0.005	0.01	0.065 (1.3×10^6)
3	0.01	0.025	0.16 (3.2×10^6)
4	0.025	0.05	0.325 (6.5×10^6)
5	0.05	0.10	0.65 (13.0×10^6)
		Schedule 2: 24-hr iv infusion	
1			0.01 (0.2×10^6)
2			0.025 (0.5×10^6)
3			0.05 (1.0×10^6)

classified as "severe" until full recovery occurred. Recombinant IFN-gamma therapy was then reinstituted at the next lower dose level (or with a 50% dose reduction for patients on dose level 1). Treatment was permanently discontinued if "severe" toxicity recurred.

Interferon

The manufacture of human rIFN-gamma was performed by Genentech, Inc. The gene for human IFN-gamma was cloned and expressed in *E. coli* by methods previously described (16). The material used in this investigation is identical in amino acid sequence to native human IFN-gamma, except for the presence of a methionine residue at the N-terminal (20). The final purity of rIFN-gamma was > 98% as determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The direct inoculation technique was used to confirm sterility. The final product contains < 0.5 ng of endotoxin per milligram of protein as determined by the limulus amoebocyte lysate assay. The specific activity of rIFN-gamma was approximately 2×10^7 units/mg of protein based on antiviral activity assessed by inhibition of encephalomyocarditis virus replication in A549 cells (human lung carcinoma cell line), corrected to the reference IFN-gamma standard Gg 23-901-530 of the National Institutes of Health, Bethesda, MD.

The interferon was provided as a sterile lyophilized powder, which was reconstituted in sterile water. For the 6-hour iv infusion, interferon was dissolved in 250 ml of 5% dextrose in water (D_5W). To prevent adherence of rIFN-gamma to the iv tubing, 2 mg/ml of human serum albumin was added to each 250-ml solution. For the 24-hour iv infusion, each patient had a central venous silastic catheter placed. The infusion was given by an autosyringe infusion pump. Interferon was reconstituted in 20 ml of D_5W containing 2 mg/ml of human serum albumin.

Pharmacology Studies

For the 6-hour iv infusion arm of the study, blood for pharmacokinetic studies was collected on Day 1. Samples were drawn preinjection and at 5 minutes (end of bolus), 30 minutes, and 1, 2, 4, 6, 6½, 7, and 8 hours. For the 24-hour iv infusion arm of the study, blood for pharmacokinetic studies was drawn at two time points: preinjection on Day 1, and 0 hour on Day 8. Blood samples were centrifuged and the serum was decanted and stored at 0°C until analysis.

Serum rIFN-gamma titers were measured by both a bioassay and an enzyme-linked immunoassay (ELISA) at Genentech, Inc. The bioassay was performed using an antiviral cytopathic effect as described previously (21), with the human lung cancer cell line A549 as a target of encephalomyocarditis virus. The 50% endpoint was determined and the interferon titer was expressed as the reciprocal of that dilution. All samples were corrected to the reference IFN-gamma standard Gg 23-901-530 of the National Institutes of Health. A solid-phase ELISA was performed using a sandwich technique with a monoclonal/polyclonal antibody system to rIFN-gamma, one of which was conjugated to a horseradish peroxidase label.

Interferon Antibody Assays

The presence of antibodies to rIFN-gamma was determined on blood samples obtained before study and 1 and 28 days after completion of the study, as well as every 4 weeks for those patients who were maintained on interferon after the initial 4 weeks. Testing for antibodies was done by both a neutralization assay and a radioimmunoassay. The neutralization assay consisted of a modification of the bioassay, described above, in which neutralization of the antiviral effect of interferon containing samples was measured. The radioimmunoassay was performed by incubating the patient's serum with [^{125}I]-labeled rIFN-gamma followed by immunoprecipitation with goat anti-human IgG. The radioimmunoassay is approximately ten- to 100-fold more sensitive than the neutralization assay for equivalent epitopes (Genentech, Inc, data on file).

RESULTS

Side Effects: 6-Hour Iv Infusions of rIFN-gamma

Twenty-one patients received rIFN-gamma by 6-hour iv infusion (table 2). The patients included nine men and 12 women, with a median age of 52 years (range, 37–71).

Most patients experienced fever, chills, myalgias, and fatigue (table 3), with escalation in dose correlating with increasing severity of symptoms. In general, symptoms occurred within 30 minutes to 2 hours after starting the infusion, and persisted for approximately 24 hours. Anorexia and mild nausea were common, although vomiting occurred in only two patients. Self-limiting diarrhea accompanied about 20% of the courses of interferon

TABLE 2.—Patient diagnosis

Diagnosis	No. of patients	
	6-hr iv infusion	24-hr iv infusion
Renal cell carcinoma	3	18
Breast carcinoma	5	4
Melanoma	0	7
Colon carcinoma	1	4
Lung carcinoma	0	4
Sarcoma	3	1
Gastric carcinoma	0	2
Well-differentiated lymphocytic lymphoma	2	0
Chronic lymphocytic leukemia	2	0
Smouldering leukemia	2	0
Neuroblastoma	0	1
Basal cell carcinoma	1	0
Nodular poorly differentiated lymphoma	1	0
Chronic myelogenous leukemia	1	0
Total	21	41

TABLE 3.—Side effects associated with iv rIFN-gamma*

Side effects	Dose in mg/m² (No. of patients)								
	24-hr infusion				6-hr infusion				
	0.005 (2)	0.01 (17)	0.025 (24)	0.05 (7)	0.016 (2)	0.065 (5)	0.16 (13)	0.325 (14)	0.65 (2)
Fever (> 38.3°C)	2*	15	22	7	1	5	13	14	2
Chills	2	13	20	7	1	5	13	14	2
Fatigue	2	13	20	5	1	5	13	14	2
Myalgias		8	13	3	1	1	4	4	2
Arthralgias		0	0	0	0	0	0	0	2
Gastrointestinal toxicity									
Nausea and/or vomiting		12	16	5	2	2	9	9	2
Diarrhea		4	4	1	0	1	4	2	0
Bleeding		1	0	0	0	0	0	0	0
Headache		13	20	6	0	3	4	5	0
Hepatic toxicity†		3	9	3	0	2	3	7	1
Hypertriglyceridemia‡		10	21	6	1	3	9	7	2
Renal toxicity									
Increased creatinine (> 2.0 mg/dl)		0	2	0	0	0	0	0	1
Proteinuria (> 1+ on dipstick)		3	2	2	0	0	0	0	1
CNS toxicity									
Crying episodes		0	0	0	0	1	2	0	0
Akathisia		0	0	0	0	0	2	0	0
Cogwheel rigidity		0	0	0	0	0	1	0	0
Confusion		3	1	1	0	0	1	1	0

*Values = No. of patients.
†SGOT and/or alkaline phosphatase increased to 2-fold baseline level.
‡Triglyceride level increased to ≥ 1.5-fold baseline levels.

therapy. Weight loss occurred in 17 of 21 patients, with a median weight loss of 2.8 kg (range, 1.0–7.8).

At dose level 5, two patients developed severe incapacitating arthralgias, but no clinical evidence of arthritis. Blood tests for C_3, C_4, total complement, rheumatoid factor, creatinine phosphokinase, aldolase, anti-DNA antibodies, anti-smooth muscle antibodies, anti-nuclear antibodies, and anti-mitochondrial antibodies were negative. Roentgenogram of the involved joints revealed no abnormalities. Complete resolution of pain and recovery of joint function occurred within 2 weeks after stopping interferon, and initiation of steroids and a nonsteroidal anti-inflammatory agent, respectively. The second patient described above also developed renal insufficiency with a BUN/creatine of 48/4.1 mg/dl on Day 4 of therapy (dose level 5). Baseline renal function had been normal. Complete recovery occurred within 72 hours after stopping both the nonsteroidal anti-inflammatory agent and the interferon. CNS toxicity included slowing of thought processes (one patient), confusion (two), crying episodes (two), and Parkinsonian-like signs (two). Electroencephalogram in each of these patients showed generalized slowing of brain waves. Symptoms improved dramatically within 48 hours after stopping interferon, and resolution was usually complete in 3–4 days. One patient with akathisia showed marked improvement after benztropine injection.

Cardiorespiratory problems developed in a single patient. This 69-year-old woman had a history of coronary artery disease and smouldering leukemia that had recently progressed to an acute phase. She complained of chest pain and shortness of breath 2 hours after starting the iv infusion at dose level 3. Interferon was discontinued and vigorous supportive measures were initiated. Nevertheless, cardiorespiratory failure and death ensued several hours later. Autopsy revealed extensive infiltration of the lungs, liver, spleen, kidneys, and lymph nodes by leukemic cells. Pulmonary edema was present, but there was no evidence of a myocardial infarct.

A dose-related reduction in absolute granulocyte counts was observed (fig 1). Granulocytopenia was evident within 24 hours after starting interferon and was uniformly reversible within 2–4 days after interruption of therapy. No incident of infection occurred. Lymphocyte, platelet, and reticulocyte counts did not change significantly.

A greater than twofold increase in liver enzymes occurred in 30%–50% of patients treated at each of dose levels 2–5 (table 3). However, hepatic toxicity was not dose-limiting in any patient on this arm of the study.

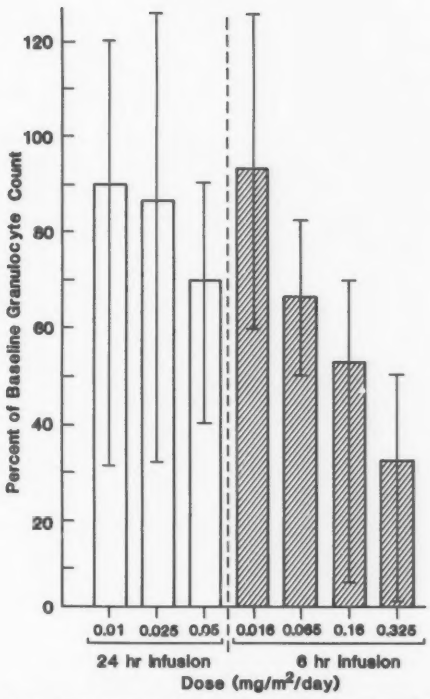

FIGURE 1.—Granulocyte counts after iv administration of rIFN-gamma. Values shown are the medians and range of the granulocyte counts observed on Day 5, expressed as a % of baseline counts.

Furthermore, enzymes consistently returned to baseline values by the end of the 7-day rest period between each of the 10-day interferon courses. Elevation in triglyceride levels occurred in the majority of patients; median increase was 67 mg/dl (range, −60 to 160).

The beta$_2$ microglobulin protein expressed on all cells as part of the human leukocyte antigen complex was quantitated by radioimmunoassay. Data are shown in figure 2. Beta$_2$ microglobulin concentration increased by Day 5 of therapy in the majority of patients.

Side Effects: 24-Hour Iv Infusions of rIFN-gamma

Forty-one patients were treated by continuous iv infusion (table 2). There were 29 men and 12 women; median age was 52 years (range, 26–71).

As with the 6-hour infusion regimen, the most common side effects were fever, chills, fatigue, anorexia, and nausea (table 3). Fever and chills often diminished significantly after the first week of therapy, whereas fatigue persisted or worsened. Vomiting and diarrhea, when present, were mild and not dose-limiting in any patient. Weight loss occurred in 28 of 41 patients, with a median loss of 3 kg (range, 1–6) in these patients. One patient with a history of two previous major gastrointestinal bleeding episodes developed melena, requiring multiple blood transfusions. Endoscopy revealed diffuse gastritis. Treatment with vasopressin, cimetidine, and antacids resulted in complete recovery.

The median decrement in granulocyte counts observed in patients treated with 0.05 mg/m^2/day of interferon (dose level 3) was 30% (fig 1). At lower doses, granulocyte counts remained unchanged. In spite of normal granulocyte counts, gram-negative sepsis occurred in three patients. Vigorous iv hydration and broad spectrum antibiotic therapy resulted in complete recovery in two of these patients. The third patient required surgical repair of an enteropleural fistula. We have not observed sepsis, even in severely granulocytopenic patients, after im injection (22) or after 6-hour iv infusion of rIFN-gamma. Therefore, we suspect that infection in two of 41 patients treated with 24-hour infusion may have been due to contamination during handling of their indwelling catheter or autosyringe delivery system. Severe sluggishness and/or confusion occurred in four patients. Electroencephalogram revealed diffuse slowing of brain waves. All patients recovered completely after interferon was stopped. Treatment with methylphenidate hydrochloride, 10 mg orally three times daily, was effective in ameliorating fatigue and sluggishness in a single patient for whom it was prescribed.

Renal insufficiency occurred in two patients, both of whom were receiving 0.025 mg/m^2/day of interferon. Peak BUN/creatinine levels were observed on Days 24 and 42 of therapy and were 75/5.6 mg/dl in one patient and 54/6.6 mg/dl in the second patient. Urinalysis revealed proteinuria of 14 and 11 g/day, respectively.

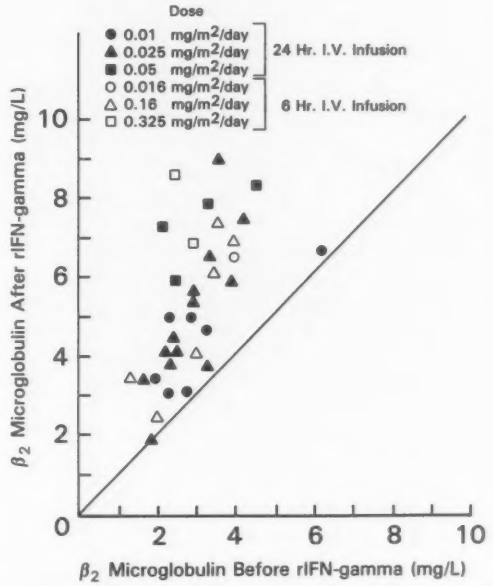

FIGURE 2.—Comparison of B_2-microglobulin levels preinjection and on Day 5 of iv administration of rIFN-gamma.

Blood tests for renal function had been normal within 1 week prior to development of the above abnormalities. Both patients remained asymptomatic, and renal function returned to baseline values within 10 days after discontinuation of interferon.

Liver function abnormalities, ie, increased serum glutamic-oxaloacetic acid and alkaline phosphatase but not bilirubin, were common (table 3). However, hepatic toxicity was dose-limiting in only one patient. As in the 6-hour infusion arm of the study, liver function returned to normal within 1 week after discontinuation of interferon. Elevation in triglyceride levels occurred in most patients. The median increase was 90 mg/dl (range, −6 to 800).

As in the 6-hour iv infusion regimen, most patients for whom data were available showed an increased $beta_2$ microglobulin by Day 5 of the study (fig 2). Values remained elevated on Day 28.

Maximum Tolerated Dose

The maximum tolerated dose was defined as one dose level below the dose at which greater than one-third of patients had toxic effects that necessitated dose reductions. None of six patients who started treatment at dose level 3 of the 6-hour iv infusion developed toxic effects that necessitated dose reduction. In contrast, five of six patients who started treatment at dose level 4 required dose reductions because of side effects as follows: fever, chills, and/or severe fatigue (three); confusion (one); and granulocytopenia (one). Therefore, the maximum tolerated dose of the 6-hour iv infusion was determined to be 0.16 mg/m^2/day.

On the 24-hour iv infusion arm, four of 14 patients who were started at a dose of 0.01 mg/m^2/day (dose level 1) required dose reductions or discontinuation of therapy. The other ten patients tolerated interferon with minimal change in performance status. At the next higher dose level (0.025 mg/m^2/day), eight of 20 (40%) patients required dose reductions or discontinuation of therapy because of various toxic effects: fever, chills, and/or severe fatigue (four); sepsis (one); headache (one); and renal insufficiency (two). Therefore, the maximum tolerated dose for 24-hour iv infusion of rIFN-gamma was determined to be 0.01 mg/m^2/day.

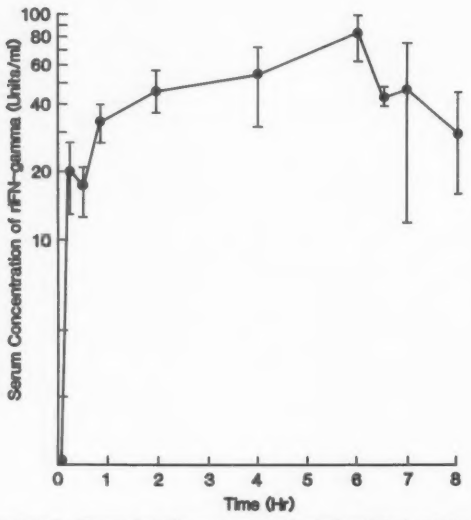

FIGURE 3.—Serum interferon concentrations of antiviral activity with 6-hr iv infusions of rIFN-gamma. Values shown are mean of samples obtained from 6 courses of treatment at dose level 4. Bars = SE.

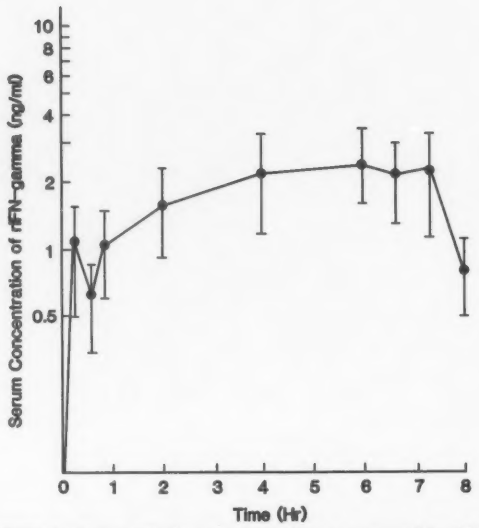

FIGURE 4.—Serum interferon concentrations as measured by ELISA with 6-hr iv infusions of rIFN-gamma. Values shown are mean of samples obtained from 6 courses of treatment at dose level 4. Bars = SE.

Pharmacology Data

The serum levels of rIFN-gamma achieved during six courses of treatment at dose level 4 of the 6-hour iv infusion regimen are shown in figures 3 and 4. (Data were available on two to six samples at each time point.) The 0.025-mg/m^2 bolus dose resulted in a mean concentration of 20.5 units/ml (bioassay) or 1.1 ng/ml (ELISA). The mean concentration maintained over the 6-hour period ranged from 18 to 83 units/ml as measured by bioassay or 0.64 to 2.4 ng/ml according to the ELISA. Although in most patients titers of rIFN-gamma dropped below detectable levels within 1 hour after stopping the infusion, in one patient levels remained very high, thus accounting for the persistent mean titers at Hours 7 and 8. Pharmacology data were not available for patients at dose level 5 because of difficulty drawing blood from these two patients. Serum titers of rIFN-gamma were below the limits of sensitivity of both the bioassay (40 units/ml) and the ELISA (0.4 mg/m!) at dose levels 1–3.

On the 24-hour iv infusions, serum rIFN-gamma titers

were below the limits of sensitivity of both assays at all dose levels.

Interferon Antibody

Data on antibody levels at baseline and 1 day after completion of study were available for nine patients on the 6-hour infusion arm and for all 41 patients on the 24-hour infusion arm. Data at 28 days after study completion were available for seven patients on the 6-hour infusion and for 28 patients on the 24-hour infusion. Since some patients had samples drawn for antibody testing at several time points, data on a total of 148 samples were available. Antibodies to rIFN-gamma were not detected in any patient, at any time point, by either the neutralization or the radioimmunoassay.

Tumor Response

On the 6-hour iv infusion, 19 of 21 patients received at least one 10-day course of therapy and 11 of 21 patients went on to receive a second course. These patients showed either no response (11 patients) or progressive disease (eight patients). On the 24-hour iv infusion, 40 of 41 patients received at least 1 week of therapy. One patient with a large locally recurrent renal cell carcinoma achieved a partial remission lasting 2 months. A minor response was observed in three patients whose diagnoses were lung carcinoma (one) and renal cell carcinoma (two). The rest of the patients had either no response (22 patients) or progressive disease (14 patients).

DISCUSSION

The major aims of this study were to ascertain the biological effects, tolerance, and pharmacokinetics of 6- and 24-hour iv infusions of rIFN-gamma. The toxicity profile of iv rIFN-gamma is qualitatively similar to that of rIFN-alpha (23), with the major dose-limiting side effects being fever, chills, and severe fatigue. Renal and neurological side effects occurred in $< 10\%$ of patients and were reversible. The maximum tolerated dose for the 24-hour iv infusion was 0.01 mg/m^2/day; for the 6-hour iv infusion, it was 0.16 mg/m^2/day. Therefore, increasing the length of infusion from 6 to 24 hours decreased the total daily dose tolerated by tenfold.

Vadhan-Raj et al (24) reported a significantly higher maximum tolerated dose (0.5 mg/m^2/day) for the same interferon preparation given by 6-hour iv infusion (without prior bolus injection) for 5 days/week for 2 weeks. Two reasons could account for the discrepancy in tolerance between their study and ours: (*a*) the loading dose given to patients in our study resulted in the achievement of plateau serum interferon levels almost immediately; and (*b*) the daily administration of interferon for 10 days without an intervening 2-day rest period could have decreased the tolerance in our patients.

Granulocytopenia occurred during this study at doses $\geq$ 0.05 mg/m^2/day, whereas granulocytopenia has not been observed after doses as high as 2.5 mg/m^2 after 5-minute iv bolus administration (17). Given the short half-life of iv rIFN-gamma (about 30 minutes) (17), these observations suggest that prolonged exposure to this molecule may be an important factor in stimulation of the cellular mechanisms which mediate rIFN-gamma-induced symptoms and granulocytopenia in vivo. These results are consistent with in vitro work showing that activation of the antiviral state in cells occurs only after several hours of incubation with rIFN-gamma (18). In contrast, activation of cells by IFN-alpha is triggered within minutes (18). The reasons for this difference between the interferons are unclear, but may reflect different molecular mechanisms of action mediated via the unique group of polypeptides known to be induced by each of the interferons (25).

Hypertriglyceridemia occurred frequently during this study. In contrast, changes in triglyceride level are not seen after IFN-alpha therapy (26). Our recent work has revealed that the mechanism of rIFN-gamma-induced hypertriglyceridemia involves impaired triglyceride removal; very low density lipoproteins are increased and the key enzyme of triglyceride metabolism, lipoprotein lipase, is decreased (27). In light of rIFN-gamma's potent macrophage activating effects, it is of interest that a similar hypertriglyceridemic state has been described in animal models and attributed to the monokine, tumor necrosis factor (28–30).

In vitro, IFN-gamma is a potent modulator of human leukocyte antigen and beta$_2$ microglobulin expression (31). As shown in figure 2, rIFN-gamma also resulted in a marked increase in beta$_2$ microglobulin protein in vivo, even at low dose levels.

Sustained serum concentrations of rIFN-gamma were achieved only at doses of 0.325 mg/m^2/day of the 6-hour infusion. Dose-limiting systemic side effects, as well as granulocytopenia, hypertriglyceridemia, and an increase in beta$_2$ microglobulin protein, occurred at much smaller doses. Therefore, serum concentrations of rIFN-gamma below the limits of sensitivities of our assays (40 units/ml for the bioassay and 0.4 ng/ml for the ELISA) are capable of eliciting a broad spectrum of biological activities in man.

Neutralizing antibodies develop in about 10% of cancer patients treated with rIFN-alpha, and may abrogate the biological activity of this agent (32). Antibody to rIFN-gamma did not develop in any patient on this study. Furthermore, antibody has not been detected in any of the approximately 300 rIFN-gamma patients who have been tested (Genentech, Inc, unpublished observations). Therefore, rIFN-gamma may be less immunogenic than rIFN-alpha.

During the short period of evaluation in this study, there was evidence of a partial remission in one patient with renal cell carcinoma, and minor responses in three patients whose diagnoses included renal and lung carcinoma. This study is part of a larger evaluation of the effect of various schedules of rIFN-gamma in renal cell carcinoma, which will be reported separately.

In conclusion, we have demonstrated that iv rIFN-

gamma is tolerated with minimal change in performance status at doses ≤ 0.01 mg/m^2/day for 24-hour infusions and ≤ 0.16 mg/m^2/day for 6-hour infusions. However, patients entered on 24-hour infusions require extreme caution in sterile handling of their catheters and careful monitoring for changes in fever pattern suggestive of infection. Prolonged infusions elicited a wide range of biological effects, including fever and chills, granulocytopenia, changes in lipid metabolism, and modulation of β_2-microglobulin. However, these various biological activities showed differential sensitivity to length of infusion and dose of interferon. On the 24-hour infusion, dose-limiting systemic symptoms occurred at one-fifth the dose necessary to produce granulocytopenia, whereas on the 6-hour infusion, granulocytopenia occurred at less than one-half the dose necessary to produce dose-limiting systemic symptoms. The absence of granulocytopenia at the maximum tolerated dose of the 24-hour iv infusion raises the possibility that this regimen produces dose-limiting systemic symptoms at doses below those needed to produce antitumor effects. However, since other biological activities are evident with this regimen, and since granulocytopenia and/or other laboratory parameters have not been definitively correlated with the response pathways responsible for interferon-induced tumor regression, this possibility remains speculative. This investigation will form the framework for phase II efficacy studies of iv rIFN-gamma.

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Phase I Study of Recombinant β ser 17 Interferon in the Treatment of Cancer[1,2]

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Fifteen patients with advanced malignancy were treated with escalating doses of recombinant β ser 17 interferon (IFN). Doses ranging from 0.006 to 500 × 10^6 units/m^2 were administered according to a dosage escalation scheme by iv push twice weekly (starting 1 week after an initial dose) for a planned minimum of 5 weeks, to be continued as a function of response. Toxic effects were broad in scope but generally low in grade. They included fever, malaise, leukopenia, proteinuria, nausea/vomiting, diarrhea, and mild elevations of serum transaminases and creatinine. In one patient, transient hypotension with bradycardia ensued. Malaise and fever increased somewhat with increasing dose. Doses of up to 500 × 10^6 units/m^2 were tolerated without severe toxicity. A maximum tolerated dose was not defined. IFN pharmacokinetics followed a biphasic decay curve, with a distribution phase α-half-life of 9 minutes and an elimination phase β-half-life of 103 minutes. Anti-IFN antibodies by the ELISA technique were present in seven of 15 patients. Presence of antibody did not correlate with toxicity or response. 2′,5′-Adenylate synthetase levels were increased 2 and 24 hours after the initial dose, with a trend toward higher increments with higher doses. Minimal antitumor responses were seen in two patients with melanoma. [Cancer Treat Rep 70:1365–1372, 1986]

Interferons (IFNs) have been shown to have antiviral and antitumor properties, both in experimental systems and in man (1–4). Possible mechanisms of antineoplastic activity include direct tumor cell cytotoxicity, indirect antineoplastic effects mediated via immunomodulation, or, possibly, induction of malignant cell differentiation.

The three classes of IFNs can be classified antigenically as α, β, and γ. α-IFNs have received substantial study in phase I and II trials (5–9). Native (fibroblast) β-IFN differs from α-IFN in structure but is 45% homologous at the nucleotide level and 29% at the amino acid level (10). β-IFN may exert more rapid antiviral effects than α-IFN (11), and it may have greater cytotoxicity in some human tumor cell lines at equivalent antiviral titers (12–14). Phase I and II trials of low doses of crude natural β-IFN have shown toxicity similar to that of α-IFN (15–18). Recombinant β ser 17 IFN (Betaseron) is a cloned, nonglycosylated variant of natural β-IFN stabilized by the substitution of serine for cysteine at the 17 amino acid position (19). In vitro, β ser 17 IFN is equivalent or superior to natural β-IFN in antiviral, antiproliferative, and immunostimulating activity (19,20). Preliminary phase I trials have shown patient tolerance of doses ranging from 10^6 to 500 × 10^6 units, with morbidity including fever, malaise, and mild hematologic toxicity (21–23). We have conducted a phase I multiple dose trial of β ser 17 IFN administered to patients in escalating doses in an attempt to assess dose-dependent biologic effects, pharmacokinetics, and toxicity of this agent, as well as to screen for antitumor efficacy. Results of studies assessing modulation of host immunologic functions will be reported separately. This paper reports the clinical and pharmacokinetic results, as well as effects on the lymphocyte 2′,5′-adenylate synthetase levels.

MATERIALS AND METHODS

Patients

Patients met the following criteria: advanced malignancy refractory to or lacking standard therapy, ambulatory status with expected survival ≥ 12 weeks, age ≥ 18 years, no therapy in the preceding 3 weeks, no CNS metastases (CNS primary tumor did not exclude patient

[1] Received Feb 24, 1986; revised July 23, 1986; accepted Aug 4, 1986.

[2] Supported by contracts N01-CM-07439 and N01-CM-07342 (Division of Cancer Treatment) and by Public Health Service grants CA-14866 (National Cancer Institute) and RR-00865 (Division of Research Resources), National Institutes of Health, Department of Health and Human Services. R. Figlin is a recipient of an American Cancer Society Junior Faculty Fellowship JFCF 762-A.

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entry), not pregnant or infected, and no prior interferon therapy. Additionally, patients were required to have adequate renal function (creatinine $\leq$ 1.4 mg/dl), hepatic function (bilirubin $\leq$ 1.4 mg/dl and SGOT and SGPT $\leq$ 100 IU/L), and hematologic function (leukocyte count $\geq$ 3800/mm^3, granulocyte count $\geq$ 1500/mm^3, and platelet count $\geq$ 125,000/mm^3). Patients were required to have adequate cardiac, pulmonary, and digestive functions and measurable or evaluable disease. Table 1 shows the characteristics of the 15 patients entered, all of whom were evaluable for both toxicity and response. The median age of these patients was 57 years (range, 28–75); there were nine females and six males in the group. All patients entered in the study are reported. The target sample size was set at 15, as a function of the dosage escalation scheme (*see* below), and patient accrual was stopped when that target was reached.

Interferon

β ser 17 IFN (lot Nos. BP107 and BP108) was provided by Cetus Corporation and Triton Biosciences, Inc, through the National Cancer Institute. The product has high specific activity (10^8 units/mg of protein) and is > 99% pure. [α-^{32}P] ATP (0.3 Ci/mmol) was obtained from ICN pharmaceutical, Irvine, CA. All other chemicals for the conduct of 2′,5′-adenylate synthetase assay were obtained from Sigma Chemical Co (St. Louis, MO).

Schedule of Administration

Patients initially received a test dose, followed by a 1-week period for assessing single-dose biologic effects. Patients then started a 5-week, twice-weekly dose escalation schedule as shown in table 2. Patients were entered in groups of three into five different dose escalation schedules. Sequential schedules started with progressively higher entry doses. Following the initial dose escalation phase, patients were evaluated for response. Patients with evidence of progressive disease were removed from the study. Patients with stable disease continued to receive therapy at a dose of 30×10^6 units/m^2 twice weekly. Subsequently, they were taken off the study either for disease progression or (in the absence of a positive response) at the 13-week evaluation, whichever was earlier. Patients with a complete, partial, or minimal response received continuing therapy until disease progression or 1 year past the point of maximal improvement, whichever came first.

Assessment and Definition of Response

Patients were evaluated for response with physical examinations every 3 weeks. They were restaged with imaging studies of the measurable or evaluable disease after completing the dose escalation phase of therapy and every 6 weeks thereafter. When the index disease was present on chest x-ray, a chest x-ray was repeated every 3 weeks. Complete response was defined as the disappearance of all measurable and evaluable disease for at least 4 weeks. For measurable disease other than malignant hepatomegaly, partial response was defined as at least a 50% decrease in the sum of the products of the largest diameters of the indicator lesions, lasting at least 4 weeks, without the appearance of new lesions or growth of old lesions by 25%. For hepatomegaly extending $\geq$ 5 cm below the costal margin(s), partial response

TABLE 1.—Patient characteristics

Patient No.	Diagnosis	Previous chemotherapy	Previous radiotherapy	Site of measurable/ evaluable disease
1	Breast carcinoma	+	+	Liver, bones
2	Melanoma	+	–	Lungs
3	Renal carcinoma	–	–	Abdomen
4	Ewing's sarcoma	+	–	Lungs
5	Melanoma	+	–	Liver
6	Myxoid chondrosarcoma	+	–	Lungs
7	Renal carcinoma	+	–	Lungs, abdomen
8	Breast carcinoma	+	–	Lungs, chest wall
9	Renal carcinoma	+	–	Lungs, abdomen
10	Glioblastoma multiforme	+	+	Brain
11	Melanoma	+	–	Lymph nodes, lungs
12	Adenocystic carcinoma (salivary gland)	+	+	Lungs
13	Colon carcinoma	+	+	Lungs
14	Melanoma	–	–	Lungs, lymph nodes
15	Renal carcinoma	+	–	Lungs

TABLE 2.—Dose escalation schedule of β ser 17 IFN (× 10^6 units/m^2)

	Group				
	1	2	3	4	5
Week 1					
Dose 1	0.006	0.6	18	45	90
Week 2					
Dose 2	0.006	0.6	18	45	90
Dose 3	0.06	6	36	60	135
Week 3					
Dose 4	0.6	18	45	90	180
Dose 5	6	36	60	135	240
Week 4					
Dose 6	18	45	90	180	300
Dose 7	36	60	135	240	360
Week 5					
Dose 8	45	90	180	300	420
Dose 9	60	135	240	300	420
Week 6					
Dose 10	90	180	240	360	500
Dose 11	135	240	240	360	500

was defined as at least a 50% decrease in the sum of the distances of hepatic extension below the costal margin at the midclavicular lines and below the xiphoid. Minimal response was defined as unequivocal improvement not meeting criteria of partial or complete response, lasting at least 4 weeks. Disease progression was defined as the appearance of new lesions or at least a 25% increase in the sum of the products of the diameters of measurable lesions. For evaluable but not measurable disease (eg, bone lesions, effusions), clear response to therapy was classified as a positive response but not quantified.

Assessment of Toxicity

Patients were examined every 3 weeks and also questioned as to interim history of toxicity prior to each dose. Blood cell counts were obtained prior to each dose of therapy, then twice weekly for 2 weeks after therapy was discontinued. Blood chemistries were drawn prior to each dose, then every week for 3 weeks after the cessation of therapy. Routine urinalysis was performed prior to each dose and serum complement levels were checked every 2 weeks. Toxicity was graded in hematologic, hepatic, renal, gastrointestinal, cardiac, and cutaneous categories as shown in table 3.

Other Laboratories

Sera for β ser 17 IFN levels were assayed prior to therapy and at 1, 5, 10, 30, 60, 120, and 180 minutes after Dose 1. Blood was drawn from the arm opposite the site of IFN infusion. IFN levels were measured in triplicate by an antiviral cytopathic technique (23), courtesy of Cetus, Inc. When there was discordance in the triplicate values, the value occurring twice or (if no value occurred twice) the middle value was chosen as representative.

Blood samples for determination of lymphocyte 2′,5′-adenylate synthetase levels were drawn before and 2 and 24 hours following Dose 1. 2′,5′-Adenylate synthetase levels were measured according to the technique of Merlin et al (24). Briefly, plasma from heparinized blood was removed by centrifugation. The buffy coat was purified by centrifugation on Ficoll-Hypaque. The lymphocytes were counted in a Coulter counter and washed three times with cold phosphate-buffered saline and lysed at 0°C with 0.1 ml of 20 mM 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer, pH 7.5, 5 mM $MgCl_2$, 120 mM KCl, 1 mM dithiothreitol, and 10% glycerol (Buffer B) containing 0.5% Nonidet-P40 (NP-40). Cytoplasmic extracts, obtained after centrifugation for 6 minutes at 8000 × *g*, were frozen in liquid nitrogen. The extracts (5–20 μl) were mixed with 20 μl of packed poly(rI):(rC)-agarose beads and incubated for 15 minutes at room temperature. The unbound material was removed by two successive washes of 0.75 ml of Buffer B, and the reaction was started by the addition of 10 μl of 2.5 mM [α-^{32}P]ATP (0.3 Ci/mmol) and 2.5 mM dithiothreitol. After 2–20 hours of incubation at 30°C, 10 μl of supernatant was removed. The pellet was washed with 10 μl of water, and the two supernatants were mixed and treated with 6 μl of bacterial alkaline phosphatase (100 units/ml in 0.17 M Tris base) for 60 minutes at 37°C. Aliquots (2.5–10 μl) were applied on the top of 300 μl of acid alumina columns previously washed with 1 ml of 1 M glycine and 0.9 M HCl, pH 2 (Buffer A). The columns were then washed with 3 ml of Buffer A, and the eluted liquid was collected and counted directly on the 3 H channel. In every experiment, controls constituted cells which were not treated with IFN and inter-

TABLE 3.—Toxicity criteria

Toxic effect	Toxicity grade 0	I	II	III	IV
Hematologic (cells/mm^3)					
Wbc count	> 4000	3000–3999	2000–2999	1000–1999	< 1000
Granulocyte count	> 1500	1000–1499	500–1000	1–499	0
Platelet count	> 100,000	75,000–99,000	50,000–74,999	25,000–49,999	< 25,000
Renal					
BUN (mg/dl)	< 20	21–40	41–60	61–100	> 100
Creatinine (mg/dl)	< 1.2	1.2–2.0	2.1–4.0	> 4	
Creatinine clearance	Normal	> 75%	50%–74%	50%	Oliguria
Proteinuria	None	Trace or 1+	2+	3+	4+
Hepatic					
SGOT (IU/L)	< 40	41–80	81–160	> 160	Encephalopathy
SGPT (IU/L)	< 40	41–80	81–160	> 160	
Total bilirubin (mg/dl)	≤ 1.4	1.5–3.0	3.0–6.0	> 6.0	
Alkaline phosphatase (units)	≤ 133	134–250	251–400	> 400	
Gastrointestinal					
Nausea/vomiting	None	Occasional	Controlled with therapy	Not controlled	Dehydration
Stomatitis	None	Erythema	Ulcer	Ulcer, unable to eat	Dehydration
Diarrhea	None	Tolerable	Tolerable with therapy	Uncontrolled by therapy	Dehydration
Cardiovascular	Normal	Rhythm changes not requiring treatment	Rhythm change requiring treatment	Congestive heart failure, high-risk rhythm change, myocardial damage	New York Heart Association class III or IV
Functional capacity	Fully active	Light work of sedentary nature	Ambulatory self-care only	Confined to bed or chair > 50% of waking hrs	Totally confined, completely disabled

nal standards were provided from the National Cancer Institute.

Sera for IgM and IgG antibodies directed against β ser 17 IFN were collected weekly during the initial study period, then every other week during the maintenance phase. Anti-IFN antibodies were measured by an ELISA assay, courtesy of Cetus, Inc (23). The titer reported is the product of the absorbance observed in the microtiter and the reciprocal of the serum dilution used. Immunologic (lymphocyte/monocyte) function studies were also performed and will be separately reported.

RESULTS

Doses

Patients were entered sequentially into five different levels of planned dose escalation, as shown in table 2. Twelve patients received all doses as scheduled. Two patients (one each in Groups 2 and 5) received the scheduled number of induction phase injections (11) but were not fully escalated because of grade III toxicity. One patient in Group 3 withdrew from the study due to disease progression after receiving seven doses. The number of doses received and maximum dose levels achieved are shown in table 4.

Toxicity

Fever was seen in all patients but two, both of whom were in Group 1. Peak fevers tended to occur 2–10 hours after the injection and then to fluctuate and finally disappear 24–36 hours after each injection. Assessment of fevers was somewhat obscured by the use of acetaminophen (10 grains orally every 6 hours) for fevers > 39°C. Fever ≥ 38.5°C rarely occurred at doses < 18 × 10^6 units/m^2, but peak fever was not clearly correlated with either dose of entry or maximum dose level achieved. Fevers were commonly preceded by chills and were accompanied by fatigue and malaise. Malaise could occur

TABLE 4.—Maximum dose level

Group No.	Patient No.	No. of doses received	Maximum dose (× 10^6 units/m^2)
1	1	27	135
	2	130	135
	3	27	135
2	4	17	240
	5	32	36
	6	25	240
3	7	11	240
	8	11	240
	9	7	135
4	10	11	360
	11	11	360
	12	15	360
5	13	17	90
	14	11	500
	15	17	500

independently of fever and was reported by most patients who received doses $\geq 60 \times 10^6$ units/m^2. In one patient (Group 1) who entered at Karnofsky performance status 70%, pronounced malaise secondary to IFN and/or disease progression reduced him to nonambulatory status.

Hematologic toxicity, consisting solely of leukopenia, was noted in six patients. One patient (Group 5) developed grade III leukopenia after her second dose of 90×10^6 units/m^2, which abated by the time of the third dose. She continued receiving β-IFN at that same dose twice weekly without further hematologic toxicity. Four other patients (one each in Groups 1-4) developed grade I leukopenia; all of these patients manifested leukopenia between 14 and 28 days in the study. One patient entered in Group 2 developed grade II leukopenia at the 6-week evaluation point. Hematologic toxicity was sporadic, occurring in some but not all patients receiving any given dose. No significant anemia or thrombocytopenia was noted, and there were no episodes of infection attributable to hematologic toxicity.

Hepatocellular toxicity was manifested as increases in SGOT, SGPT, or alkaline phosphatase without acute hepatic pain, enlargement, or tenderness. Enzyme elevations generally occurred in the midst of therapy, then stabilized throughout the course. Of a total of 15 patients, ten had hepatic toxicity, which was grade I in six patients. Three patients developed grade II toxicity which was not dose-related (Groups 1, 2, and 4). One patient (Group 5, with maximum dose of 500×10^6 units/m^2) developed grade III toxicity with increases of SGOT and SGPT at baseline from 38 and 19 to 133 and 208, respectively. Total bilirubin and alkaline phosphatase remained in the normal range.

Nausea, vomiting, and diarrhea were fairly common, especially in patients receiving doses $\geq 135 \times 10^6$ units/m^2. Six of the ten patients reaching the maximum dose levels in Groups 1-4 developed grade I toxicity. Two of the five patients who received the two highest dose levels (360 and 500×10^6 units/m^2) had grade II gastrointestinal toxicity. One patient with grade I nausea and vomiting lost $> 10\%$ of his prestudy body weight.

Nephrotoxicity was manifest as mild reversible increases in serum creatinine or mild proteinuria. Ten of the 15 patients developed proteinuria, all measured at trace or 1+. Proteinuria was demonstrated at all initial and maximum dose levels and was not dose-dependent, related to fever, or associated with hypocomplementemia. Six of 15 patients developed mild increases in creatinine, three from Group 1, one from Group 3, and two from Group 5. All serum creatinine values remained < 2.0 mg/dl. Of the four patients with metastatic renal cell carcinoma (all status postunilateral nephrectomy), there was one patient with grade I proteinuria and another with a grade I increase in creatinine.

Mild decreases in serum Ca, PO_4, and albumin were observed. Serum Ca decreased from a pretherapy mean value of 9.93 ± 0.19 mg/dl to a value of 9.46 ± 0.23 mg/dl at the end of the induction phase. The mild decrease in Ca was significant at the $P < 0.05$ level by paired t test. This may have been primarily due to a fall in albumin (mean, 3.97 ± 0.12 mg/dl pretherapy, 3.72 ± 0.1 mg/dl at the end of induction, $P < 0.05$), since correcting the Ca for the fall in albumin (0.8 mg/dl of Ca for 1 g/dl of albumin) yielded a corrected postinduction value of 9.72 mg/dl (not significantly different than pretherapy). PO_4 fell from a pretherapy mean of 4.0 mg/dl to a postinduction therapy mean of 3.0 mg/dl ($P < 0.05$ by paired t test). Cholesterol fell from a mean value pretherapy of 202 ± 13 mg/dl to a postinduction mean value of 186 ± 13 mg/dl, but this was not statistically significant.

One patient, entered initially in Group 2 (initial dose, 0.6×10^6 units/m^2), developed grade III cardiovascular toxicity consisting of faintness, hypotension (minimum blood pressure, 68/40), and bradycardia, which rapidly responded to fluids. No evidence of myocardial damage was seen on serial ECGs or creatine phosphokinase enzymes. The patient's dose was decreased from 45 to 36×10^6 units/m^2, which she subsequently received twice weekly for an additional 14 weeks without repeated toxicity. Two other patients, entered in Group 4 (initial dose, 45×10^6 units/m^2), developed grade I cardiovascular toxicity consisting of a 30-40-point drop in systolic blood pressure unaccompanied by symptoms. Both patients responded to iv fluids acutely.

Three patients had severe headaches during therapy, often occurring simultaneously with fever. Two patients from Groups 1 and 5 had a mild multifocal skin rash and pruritis. One patient in Group 1 and one in Group 3 developed localized herpes zoster infections while receiving β-IFN therapy.

CNS toxicity, noted with some previous α-IFN preparations, was not noted in this study. Acute tumor pain shortly after injection was reproducibly noted by one patient with renal cell carcinoma.

Responses

Of the 15 patients treated, minimal responses were noted in two of the four with melanoma. One patient, entered in Group 1, showed slight reduction in four indicator lung metastases scored as a minimal response at 6 weeks. At 19 weeks, the indicator lesions had continued to decrease in size to a level consistent with partial response, but two ambiguous lesions, not clearly defined on initial radiographs, were shown to have concurrently increased in size. Treatment was continued and the indicator lesions disappeared by both routine chest radiograph and tomography. The nonindicator lesions remained unchanged until approximately 46 weeks from the start of therapy, when an increase in size in the nonindicator lesions and the appearance of new lesions were noted. The patient was continued on IFN, with a dose escalation to the highest dose reached by this patient in the initial 5-week escalation phase, 135×10^6 units/m^2 twice weekly. The patient then had complete disappearance of the new lesions (by tomography) with stability of the nonindicator lesions for 16 weeks, followed by pro-

gression of the original nonindicator lesions. He had previously received chemotherapy with bleomycin, vincristine, lomustine, dacarbazine, and vinblastine without benefit.

A second patient with melanoma metastatic to liver (Group 2) showed a minimal response at 6 weeks which persisted until 16 weeks from the start of therapy. At that point, new pulmonary metastases were noted. During the course of therapy, this patient developed bilateral breast lesions which, on biopsy, revealed only necrotic tissue. Additionally, during therapy, this patient had an intracranial hemorrhage. A resultant craniotomy with evacuation of clot was performed; a small focus of necrotic, apparently nonviable, melanoma was found.

Two other patients with melanoma were taken off study after disease progression at 6 weeks. Seven patients with other malignancies were stable at the 6-week point, but taken off study by 13 weeks for disease progression (five patients) or stable disease (two). One patient in Group 3 with recurrent renal cell carcinoma withdrew from the study after Dose 7 because of symptoms related to progressive disease.

Pharmacokinetics

The pharmacokinetics of β ser 17 IFN were evaluated in all patients following the initial dose of therapy. Three patients each were studied at 0.006, 0.6, 18, 45, and 90×10^6 units/m^2. Pretherapy β-IFN levels as well as postinfusion levels at various time points were measured. Pooled data (mean values) are shown in figure 1.

At doses $\leq 0.6 \times 10^6$ units/m^2, IFN levels were not readily detectable. Mean peak IFN levels (1 minute after injection) were 8286 units/ml for a dose of 90×10^6 units/m^2, 3467 for 45×10^6 units/m^2, and 1508 for 18×10^6 units/m^2. These three points fit the regression line formula $y = 96x - 441$, where y is the peak concentration of IFN (units/ml) and x is the dose administered ($\times 10^6$ units/m^2). At the above three doses, the serum IFN decay curve appears biphasic, with a distribution phase lasting roughly 10 minutes (α-half-life = 9 minutes: 7.8 minutes at 90×10^6 units/m^2, 12.2 minutes at 45×10^6 units/m^2, and 7.3 minutes at 18×10^6 units/m^2) and a subsequent elimination phase persisting > 3 hours (β-half-life = 103 minutes: 108 minutes at 90×10^6 units/m^2, 100 minutes at 45×10^6 units/m^2, and 101 minutes at 18×10^6 units/m^2).

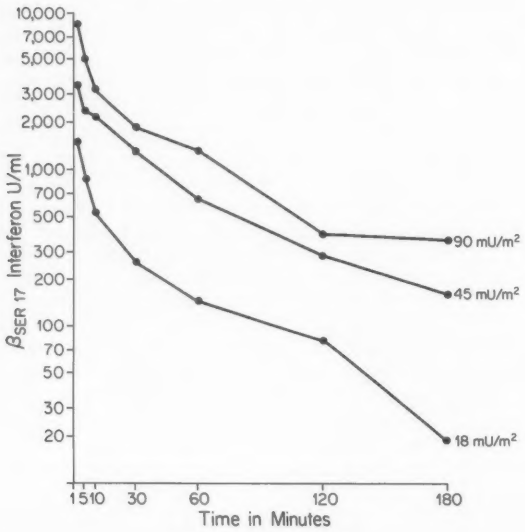

FIGURE 1.—Pooled data.

2′,5′-Adenylate Synthetase

Samples for determination of lymphocyte 2′,5′-adenylate synthetase were obtained pretherapy and then 2 and 24 hours after Dose 1. A trend toward increased 2′,5′-adenylate synthetase activity was seen at both the 2- and 24-hour time points, particularly in Groups 3–5 (doses $\geq 18 \times 10^6$ units/m^2). Mean values for each group are shown in table 5. In general, higher activity was seen at 2 hours than at 24 hours, and higher activity was noted at higher dose levels (Groups 3–5). However, there was substantial variability among patients. The 2′,5′-adenylate synthetase activity did not correlate with toxicity or response. In the two patients with herpes zoster, 2′,5′-adenylate synthetase activity was indistinguishable from that of other patients in the same group of entry.

Anti-IFN Antibodies

IgM and/or IgG antibodies were detected in seven of the 15 patients. IgM antibodies were first detectable from 1 to 6 weeks after the initial injection (median,

TABLE 5.—Mean 2′,5′-adenylate synthetase levels

Group No.	Time	Level (pmols of ATP/hr/10^6 lymphocytes)
1	Before treatment	12.6
	2 hrs after treatment	33.6
	24 hrs after treatment	23.6
2	Before treatment	15.0
	2 hrs after treatment	23.3
	24 hrs after treatment	25.0
3	Before treatment	10.7
	2 hrs after treatment	115.5
	24 hrs after treatment	48.9
4	Before treatment	14.3*
	2 hrs after treatment	122.2
	24 hrs after treatment	54.3
5	Before treatment	32.3
	2 hrs after treatment	226.0
	24 hrs after treatment	10.3†

*Single control level of 195.2 pmols of ATP/hr/10^6 lymphocytes in 1 patient was felt to be an error and was discarded. The patient had a second control value of 18.8 pmols of ATP/hr/10^6 lymphocytes, which is included.

†24-hr level was obtained in only 1 of the 3 patients.

3 weeks), and persisted for as long as 64 days. Titers ranged from 2 to 3 units when first detected to subsequent high values of 10–20 units. IgG antibodies were first detectable at 21 days after the initial injection and persisted for as long as 90 days. IgG titers ranged from 5 to 90 units on first detection, and the highest titer seen was 158 units. One patient developed only IgM antibodies, one patient developed only IgG antibodies, and five patients developed both. Development of measurable antibody correlated to some degree with both increasing initial and maximum dose levels, in that no patient in Group 1 developed antibodies. Presence of antibody did not correlate with proteinuria or skin rash, and no decreases in complement levels were observed.

DISCUSSION

We have studied β ser 17 IFN administered by iv bolus over a wide range of doses, escalating from 0.006 to 500×10^6 units/m^2. Despite that level of escalation, a maximum tolerated dose was not reached. Within the dosage range tested, there were modest hematologic, renal, hepatic, and gastrointestinal toxic effects, which were not clearly dose-related. No grade IV toxicity was seen, and only three episodes of reversible grade III toxicity were noted. This relatively mild toxicity contrasts favorably to the toxicity noted with equivalent doses of the α-IFNs (7), which have shown a similar range but greater degree of toxic effects, with maximum tolerated doses in multiple-dose trials (frequently daily im) falling in the range of $30–50 \times 10^6$ units (5) and with CNS toxicity seen at doses as low as 50×10^6 units/m^2 thrice weekly (8,25). Malaise in some α-IFN regimens has been severe and has resulted in patients' becoming nonambulatory (5). Our findings of mild to moderate toxicity with β ser 17 IFN are consistent with similar findings in other phase I studies (21–23).

β ser 17 IFN appeared to show hints of possible therapeutic activity in metastatic melanoma, with two patients showing minimal responses. Chang et al (21) have reported a partial response in a patient with melanoma receiving β ser 17 IFN by sc injection, and both nonrecombinant and recombinant β-IFNs have shown activity against a human melanoma cell line implanted in nude mice (26,27). Activity against breast cancer has previously been noted in a small multiple-dose phase I trial of natural β-IFN (15) but was not seen in the two patients with breast cancer entered in this study.

Pharmacokinetic studies suggested that serum levels of β ser 17 IFN (administered by rapid iv push) follow a biphasic decay curve, with a distribution phase lasting roughly 10 minutes and an elimination phase lasting nearly 100 minutes. The half-life figures are similar to the 10-minute α-half-life and the 44–65-minute β-half-life reported by Ratanatharathorn et al (22). While these data may argue for frequent administration or constant infusion of β ser 17 IFN, the observations that im β ser 17 IFN evokes biologic effects in the absence of detectable IFN levels (23) and that fever and malaise persist after iv β ser 17 IFN in the absence of detectable serum levels suggest that duration of drug effect may not be adequately described by the pharmacokinetics.

Although seven of the 15 patients entered developed anti-IFN antibodies, there was no evidence that this affected response or toxicity of therapy. While this study did not assess whether or not these antibodies were "neutralizing" in vitro, Hawkins et al (23) have reported only one of 17 patients with anti-β ser 17 IFN antibodies by ELISA technique to have neutralizing activity.

Lymphocyte 2′,5′-adenylate synthetase activity showed a tendency to increase 2 and 24 hours after a single dose of β ser 17 IFN. Higher activity was noted at higher dose levels, but activity did not correlate with toxicity or response. These findings are similar to those recorded in a previous α-IFN study (28) and are consistent with the findings of Chang et al (21) with sc β ser 17 IFN. Our observations of herpes zoster occurring in two patients in this trial do not support strong antiviral activity of this agent, at least for herpes zoster, as given in this intermittent schedule.

Suggestions of activity of β ser 17 IFN were seen against malignant melanoma, and the secondary response observed in the patient with melanoma who received a dose escalation after disease progression suggests the possibility of a dose-response relationship. We are currently investigating activity of (relatively) low and high dose levels of β-IFN against melanoma in a phase II trial. While we did not observe activity against other malignancies, sample size, patient characteristics, and dose/schedule limitations preclude conclusions about efficacy of β ser 17 IFN against various tumor types. Phase II studies will be needed to further investigate this issue.

We have observed mild to moderate constitutional, hematologic, renal, and hepatic toxic effects from β ser 17 IFN in this escalated, multiple-dose phase I trial. We have not defined either the maximum tolerated dose or the optimal dose/schedule from either the antineoplastic efficacy/toxicity or the biologic response modification perspectives. Future studies may help to clarify these issues.

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Clinical Pharmacology of Mitoxantrone[1,2,3]

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A pharmacokinetic study on mitoxantrone was performed within the framework of a phase II clinical trial. Serum concentrations and urinary excretion were measured using a high-performance liquid chromatography method. Four metabolites were separated in urine and three in serum. The two major metabolites cochromatographed with the synthesized monocarboxylic and dicarboxylic acids of mitoxantrone. Within 48 hours, 4.4% of the administered dose was excreted in urine as mitoxantrone, 0.5% as Metabolite 1, and 0.3% as Metabolite 2. The pharmacokinetic parameters are adequately described by a three-compartment model with a terminal half-life of 214.8 hours and a volume of distribution of 2248 L/m^2. The total-body clearance was 217 ml/min/m^2 and the renal clearance was 15 ml/min/m^2. These results suggest that mitoxantrone is sequestered in a deep tissue compartment and only slowly released. [Cancer Treat Rep 70:1373-1378, 1986]

Mitoxantrone, an anthracenedione derivative, has shown cytotoxic effects in both animal and in vitro test systems (1-7). In clinical studies, encouraging antitumor activity has been demonstrated in patients with advanced breast cancer (8-10), lymphoma (11-13), and leukemia (14-18).

Therefore, it is important to have a full understanding of the pharmacokinetic behavior of this substance. Current data are, however, controversial, with the elimination half-life varying between 1.88 hours and 42.6 hours (19-30). Such differences may have been due to the derivation of the data from studies which employed a variety of high-performance liquid chromatography (HPLC) analytical methods having a sensitivity that varied from 75 ng/ml (25) to 1 ng/ml (31). It is relatively clear that while the alpha and beta half-lives are relatively short, the gamma half-life has not been adequately established. Data from autopsy samples suggest that the elimination half-life of mitoxantrone should be much longer (20) than published in these studies. This concept is further supported by the work of James et al (32), in which the elimination half-life in monkeys was reported to be 8.5 days.

Evidence of metabolism of mitoxantrone was obtained in our earlier study (33,34), in which three metabolites were observed in the isolated perfused rat liver. Later studies in man using radiolabeled mitoxantrone demonstrated the presence of unidentified metabolites (20).

A pharmacokinetic study was performed as part of a phase II trial (35) to investigate the body distribution and elimination of mitoxantrone and to identify its metabolic pattern and is the subject of this report.

METHODS

Only patients with advanced breast cancer without any prior chemotherapy were enrolled in this study. All patients had normal renal and liver function as assessed by creatinine, BUN, bilirubin, albumin, and coagulation profile. Mitoxantrone was administered at a dose of 14 mg/m^2 as an iv infusion over 30 minutes on Day 1, and cyclophosphamide at a dose of 600 mg/m^2 iv over 30 minutes on Day 2, repeated every 4 weeks. Venous blood samples were taken immediately prior to treatment and at 10, 20, 30, 45, and 60 minutes and at 2, 4, 6, 24, and 48 hours following the infusion and on subsequent days. Serum was stabilized by the immediate addition of ascorbic acid (5% wt/vol) in 0.1 M citrate buffer (pH 3; 9 parts serum + 1 part stabilizer) as described by Reynolds et al (25) and stored at −20°C.

Urine was voided spontaneously. A total of 250 ml of double-distilled water was added to each specimen to

[1] Received Mar 20, 1985; revised July 14, 1986; accepted Aug 1, 1986.
[2] Supported by Lederle-Cyanamid, Wolfratshausen, Federal Republic of Germany, and by the Wilhelm-Sander-Foundation.
[3] Mitoxantrone and the monocarboxylic and dicarboxylic acid analogs were supplied by Medical Research Division, American Cyanamid Company, Pearl River, NY.
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prevent precipitation of urine components. All samples were kept at room temperature until analyzed.

Mitoxantrone (fig 1) for clinical use was supplied in 30-mg (2 mg/ml) vials by Lederle Laboratories, Pearl River, NY.

HPLC apparatus, chromatographic conditions, and sample cleaning were used as described elsewhere (36).

Recovery, Precision, and Detection Limit

The recovery was calculated by comparing the peak height or peak area of the added mitoxantrone to serum and urine to that of the standard added to the mobile phase. Precision and accuracy were determined by assaying duplicate serum samples on 12 different days. The detection limit of the assay was set at a response equal to two times the average noise level.

Computation of Results

Nonlinear least-square regression analysis of data was performed with the TOPFIT program (37,38); curve fitting was accomplished with a data weighting of $(C_{obs} - C_{calc})^2/C_{obs}$ for serum and $(C_{obs} - C_{calc})^2$ for urine.

RESULTS

Standard curves were linear over the 0.5–2000-ng range ($r > 0.999$). Recovery of mitoxantrone from urine and serum was > 96.3%, with a coefficient of variation < 9.3% at a concentration of 0.2 ng/ml. The coefficient of variation of the assay reproducibility at a serum concentration of 200 ng/ml measured by independent analyses in duplicate on 12 different days was 5.4%. The limit of sensitivity was 0.2 ng/ml in urine and 1 ng/ml in serum. Recovery of metabolites was determined by comparing peaks after direct injection of urine containing these metabolites into the HPLC system with those after the usual sample cleanup procedure. No loss of metabolites was observed. The stability of metabolites was checked by repeated analysis of serum samples. The concentrations of metabolites were unchanged. These substances were not formed in vitro.

Serum and urine from patients before treatment contained no peaks which occurred at the same positions as those of the compounds of interest.

Cyclophosphamide did not disturb sample cleanup and mitoxantrone measurement at 658 nm.

Figure 2 shows the chromatographic profile of urine collected at different time intervals before and after mitoxantrone administration. The retention time of mitoxantrone was 11.3 minutes. Three metabolites (Nos. 1, 2, and 3) were observed, with retention times of 5.3, 7.7, and 9.3 minutes, respectively; these were clearly separated from the solvent front, other biological constituents, and mitoxantrone. The same metabolites were detected also in serum samples. In addition, one further peak with a retention time of 14.6 minutes was observed in urine samples obtained 4 weeks after dosing.

The amount of mitoxantrone, Metabolite 1, and Metabolite 2 excreted in urine is expressed as percent of dose in table 1. Metabolite 3 was detected only in the first voided samples and accounted for 0.04% ± 0.1% of the dose within 4 hours. After purification by preparative HPLC, all metabolites were observed to be blue colored, except the reddish brown material which eluted with a retention time of 14.6 minutes.

The synthesized dicarboxylic and monocarboxylic acid analogs of mitoxantrone (fig 1), which are metabolites of mitoxantrone as recently reported by Chiccarelli et al (39), were eluted with retention times identical to those of Metabolites 1 and 2, respectively.

The pharmacokinetic parameters were estimated using both urinary and serum values. The combined data were best described by an open three-compartment model. The results of the pharmacokinetic analyses are listed in table 2. The plasma disappearance curve and urinary excretion for Patient 6, Cycle 1, are shown in figure 3.

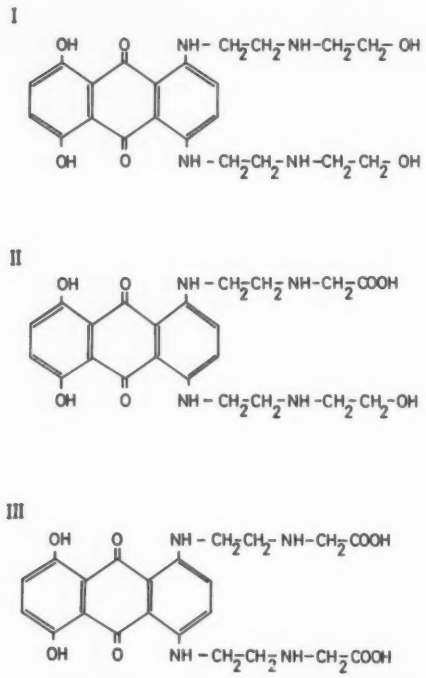

FIGURE 1.—Chemical structure of mitoxantrone (I) and its monocarboxylic acid (II) and dicarboxylic acid (III) analogs.

DISCUSSION

The efficacy and side effects of mitoxantrone assessed in this study have been previously reported (35). In general, it was found that the combination of mitoxantrone and cyclophosphamide was active and well tolerated.

The present pharmacokinetic study employed analytical methods which allowed detection of mitoxantrone in

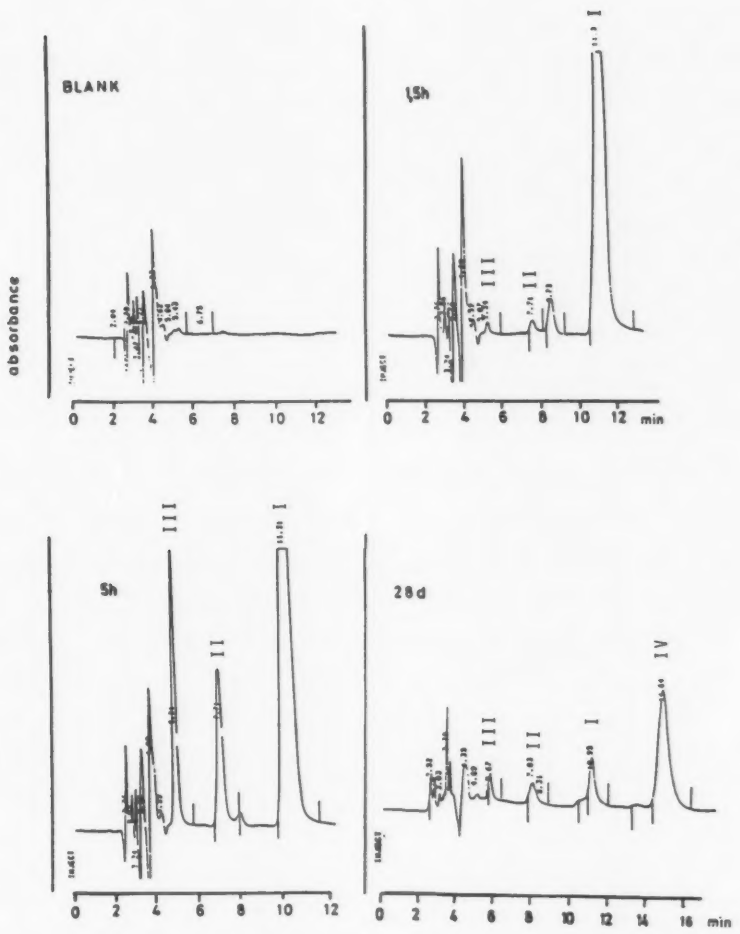

FIGURE 2.—HPLC chromatogram of urine samples collected after treatment with 14 mg/m^2 of mitoxantrone (Patient 1, Cycle 3). Top left: blank before treatment. Sample at 0–1.5 hrs after treatment shows mitoxantrone (I) as dominant peak at retention time (RT) 11.31. Metabolite 1 (III) (RT 5.34) and Metabolite 2 (II) (RT 7.71) were detected in small amounts. Metabolite 3 (RT 9.73) is predominant. The sample from period 1.5–5 hrs shows Metabolites 1 and 2 in higher amounts. 28 days after dosing, mitoxantrone and Metabolites 1 and 2 are still present, but a new peak (IV) occurred at RT 14.64.

TABLE 1.—Cumulative urinary excretion*

	Mitoxantrone			Metabolite 1			Metabolite 2		
	12 hr (n = 16)	24 hr (n = 15)	48 hr (n = 9)	12 hr (n = 16)	24 hr (n = 15)	48 hr (n = 10)	12 hr (n = 16)	24 hr (n = 15)	48 hr (n = 10)
Maximum	5.5	6.0	7	0.58	0.75	0.87	0.33	0.45	0.34
Minimum	1.15	1.5	3.2	0.03	0.04	0.14	0.03	0.04	0.19
Mean	3.07	3.64	4.41	0.26	0.33	0.54	0.19	0.22	0.33
SD	1.26	1.24	1.29	0.16	0.2	0.23	0.09	0.1	0.08

*Expressed as % of dose.

TABLE 2.—Pharmacokinetic parameters

Patient No. (Cycle No.)	Half-life (hrs)			Vss* (L/m^2)	AUC† ($\mu g \times hr/ml$)	Clearance ($ml/min/m^2$)	
	α	β	γ			Total	Renal
1 (2)	0.18	4.23	201.0	2059	1.46	137.9	13.9
2 (9)	0.18	10.95	196.6	2272	1.07	222.0	—
3 (5)	0.10	0.22	300.1	1710	3.31	70.9	7.7
4 (3)	0.10	0.49	197.0	1997	1.74	132.4	14.9
5 (5)	0.15	1.07	138.6	1916	0.60	331.1	—
6 (1)	0.15	0.93	345.6	3841	1.49	158.2	16.5
7 (8)	0.13	3.94	124.6	1942	0.51	466.0	23.9
Mean	0.14	3.12	214.8	2248	1.45	216.9	15.4
SD	0.03	3.54	74.8	669	0.87	127.2	5.2

*Vss = volume of distribution in steady state.
†AUC = area under curve.

the nanogram range and the separation of its metabolites.

Two of the four separated peaks had retention times identical to those of the monocarboxylic (Metabolite 2) and dicarboxylic (Metabolite 1) acid derivatives of mitoxantrone. These materials have been described by Chiccarelli et al (39,40) as metabolites isolated from the urine of leukemia patients and dogs and the bile of rats. The structural analyses done by negative ion chemical ionization mass spectrometry would still benefit from verification by nuclear magnetic resonance (NMR) examinations. However, the small amounts of urine-excreted metabolites and paramagnetic and zwitterion characteristics would yield further problems. Until NMR spectra are available, it would be more prudent to consider these substances as proposed metabolites. The

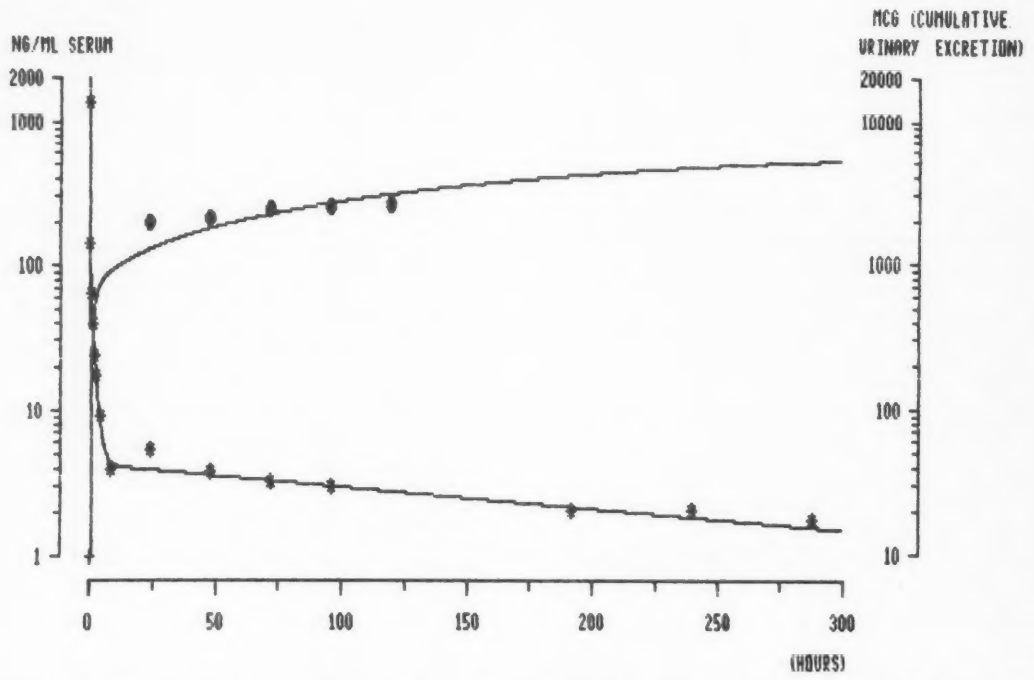

FIGURE 3.—Computer-fitted curve of mitoxantrone serum concentration and cumulative urinary excretion vs time for Patient 6, Cycle 1 (* = serum; ● = urine).

additional two metabolites (Nos. 3 and 4) described here have not been previously reported in man. Analysis of their chemical structure is ongoing.

The appearance of these four metabolites is not dependent upon the administration of cyclophosphamide, since Metabolites 1 and 2 have been described by Chiccarelli (39) in patients treated only with mitoxantrone, and our own early preliminary work demonstrated the presence of all four metabolites in breast cancer patients treated with mitoxantrone as the sole agent.

Excretion of mitoxantrone and Metabolites 1 and 2 was quite variable, and the excretion pattern (ie, the ratio of metabolite to parent drug) was also variable, ranging from 1% to as much as 33% for Metabolite 1 and from 1% to 12% for Metabolite 2. While no explanation for the variability is immediately apparent, it is conceivable that patient status, alternative metabolic pathways, and capacities of other excretory pathways may all contribute to the observed wide range of values for urinary excretion.

The calculated renal clearance was 26 ml/min and accounted for 4.4% of the dose in 48 hours. These results are in close agreement with those previously reported (20,41). The observation in man that 28% of the dose is excreted in the feces (20) within 5 days, as well as the high rate of biliary excretion in the rat (34,40), supports the concept that bile may be the major route for the elimination of mitoxantrone.

The total-body clearance had a mean value of 217 ml/min/m^2 and not only represents renal and biliary excretion and metabolism but also includes the disappearance of drug from the plasma into the tissues.

The disappearance of mitoxantrone from serum is adequately described by a three-compartment open model. The rapid alpha distribution phase with a half-life of 0.14 hours is likely to represent the plasma equilibrium, binding to endothelium, and penetration into the formed elements of blood. Alberts et al (20) have demonstrated that mitoxantrone binds reversibly to blood-formed elements. The estimated beta half-life is 3.1 hours and is associated with a redistribution of the drug from the formed elements and surfaces into the tissues. The terminal half-life in the present study was 214.8 hours (approximately 9 days). The contribution to the area under the curve (AUC) made during the terminal phase is equal to 70% of the total area under the serum AUC. Previously reported (20,22,23,27,28) terminal half-life values have been much shorter [1.88–42.6 hours (table 3)], which might reflect the limitations of assay sensitivity or differences in data handling by utilizing only plasma concentrations. It is also possible that in our study the administration of cyclophosphamide 24 hours after mitoxantrone may alter the elimination of mitoxantrone.

Alberts et al (20) reported that ^{14}C-radiolabeled mitoxantrone-related material was present in relatively high concentrations in several tissues taken at autopsy 35 days after drug administration. Roboz et al (41) measured mitoxantrone by a specific HPLC method in organs of a patient who died 9 days after the last day of drug administration. The tissue concentrations were approximately 200-fold those in the peripheral blood. These results suggest a "deep" tissue compartment with slow release which is consistent with the long terminal half-life reported here. The very large mean value of the volume of distribution (2248 L/m^2) suggests that much of the mitoxantrone is sequestered in tissue and only slowly released, as also indicated by the long elimination half-life. This sequestration may contribute to the safety profile of mitoxantrone since the binding may be largely nonspecific and thereby effectively store the drug in a nontoxic (nonactive?) form.

TABLE 3.—Published pharmacokinetic data of mitoxantrone

Author (Ref No.)	Half-life (hrs) α	β	γ	Comments
Alberts et al (20)	0.1	1.0	42.6	Adults
Neidhart et al (22)	—	—	1.88	—
Miser et al (23)	0.057	0.378	3.87	Children
Savaraj et al* (27)	0.228	37.4	—	Adults
	0.398	70.7	—	Impaired liver function
Smyth et al (28)	0.16	2.0	17.0	—

*2-compartment model.

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Model for Estimation of Clinically Achievable Plasma Concentrations for Investigational Anticancer Drugs in Man[1,2]

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A major problem related to in vitro testing of new investigational anticancer compounds is the lack of accurate pharmacokinetic data for the drugs in man. Based on the concept of a relationship between certain toxicologic endpoints in animal systems and maximally tolerated doses in man, we hypothesized that a comparable agreement might exist between these experimental animal toxicology data and clinically achievable peak plasma concentrations (PPCs). A retrospective analysis of the known data pairs of 28 commonly used cytotoxic compounds supports the existence of a reasonably good correlation between ip LD50 values (Pearson test) in nontumored mice and PPCs in man ($r^2 = 0.501$; $P < 0.0001$). Our data suggest that by use of the resultant statistical regression model a rational starting point can be selected for in vitro screening of entirely new agents for which human PPCs are not available. Additionally, application of this approach may also prove useful in relation to selecting in vitro doses for chemosensitivity assays intended for predictive correlation with clinical response in cancer patients. [Cancer Treat Rep 70:1379–1382, 1986]

Well-accepted criteria for defining the in vitro antineoplastic activity of a totally unknown agent in preclinical screening systems are currently unavailable. Ideally, such criteria would take into account clinical pharmacokinetic parameters such as peak plasma level or concentration × time product. Unfortunately, this pharmacokinetic information is not known for most investigational compounds.

Based on the concept of a relationship between certain toxicologic endpoints in animal systems and maximally tolerated doses in man (1,2), we assumed that there might exist a comparable agreement between these animal toxicity data and clinical pharmacokinetic parameters. To demonstrate that relationship, a retrospective comparative analysis of ip LD50 values in mice and known clinically achievable peak plasma concentrations (PPCs) in man was performed for 28 anticancer agents. Our data indicate that by use of the resultant regression model a rough approximation of PPCs in man can be obtained. The proposed statistical model might thus yield relevant information for more correctly interpreting the true significance of the in vitro antitumor activity of a new compound.

MATERIALS AND METHODS

The cytotoxic antitumor agents selected for analysis were confined to those for which acute animal toxicology data as well as human pharmacokinetic parameters were available. LD50 values (mg/kg) after ip single bolus administration in nontumored mice were provided by the Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD, and by Dr. J. Kuhn, The University of Texas Health Science Center, San Antonio. The LD50 was used because it has been considered the most reliable category of lethal doses (3). The corresponding clinical PPCs (μg/ml) of the 28 drugs considered in this study were obtained from the published literature (table 1). Whenever the serum concentration of a drug had been determined for more than one dose or one schedule, the mean PPC that was measured with the most toxic regimen was utilized.

[1] Received Oct 17, 1985; revised May 28, 1986; accepted Aug 1, 1986.

[2] Supported by grant J0042 from the Fond zur Foerderung der Wissenschaftlichen Forschung, Vienna, Austria; and by contracts N01-CM-17497 and N01-CM-57737 (Division of Cancer Treatment) and Public Health Service grants CA-21839, CA-17094, and CA-27733 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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TABLE 1.—Acute animal toxicology data* and clinically achievable PPCs of various anticancer compounds

Drug	LD50 (mg/kg)	PPC (μg/ml)	Dose	Route	Ref No.
Dactinomycin	1.4	0.08	0.015 mg/kg	Iv	8
Bisantrene	245.0	5.00	260.00 mg/m^2	Iv	9
Bleomycin	303.0	3.00	15.00 U/m^2	Iv	8
Busulfan	160.0	0.83	6.00 mg	Oral	10
Carmustine	42.0	1.97	95.00 mg/m^2	Iv	8
Chlorambucil	81.0	1.10	0.60 mg/kg	Oral	8
Cisplatin	26.8	2.49	100.00 mg/m^2	Iv	8
Cyclophosphamide	609.0	29.40	10.00 mg/kg	Iv	8
Cytarabine	3700.0	250.00	10.00 mg/kg	Iv	8
Daunorubicin	8.6	0.41	100.00 mg/m^2	Iv	8
Doxorubicin	35.0	0.60	60.00 mg/m^2	Iv	8
Dacarbazine	1900.0	15.28	250.00 mg/m^2	Iv	8
Etoposide	105.0	34.18	290.00 mg/m^2	Iv	8
5-Fluorouracil	171.0	60.00	15.00 mg/kg	Iv	8
Floxuridine	650.0	73.80	5.7×10^{-3} M/hr	Intra-arterial	11
Hexamethylmelamine	452.0	20.60	200.00 mg/m^2	Oral	8
Hydroxyurea	9.1	48.29	1000.00 mg/m^2	Oral	8
Ifosfamide	565.0	221.96	130.00 mg/kg	Iv	8
Melphalan	29.6	3.38	0.60 mg/kg	Iv	8
6-Mercaptopurine	523.0	18.00	500.0 mg/m^2	Iv	8
Menogaril	47.0	0.16	126.00 mg/m^2	Iv	12
Methotrexate	69.0	2.75	30.00 mg/m^2	Iv	8
Mitomycin	8.5	1.50	20.00 mg	Iv	8
Mitoxantrone	11.3	0.25	6.00 mg/m^2	Iv	13
PALA	4000.0	20.00	200.00 mg/m^2	Iv	8
Thiotepa	27.0	19.90	20.00 mg	Iv	14
Vinblastine	6.8	0.78	0.20 mg/kg	Iv	8
Vincristine	5.8	0.37	0.025 mg/kg	Iv	8

*Ip LD50 values in nontumored Swiss/BDF$_1$ mice.

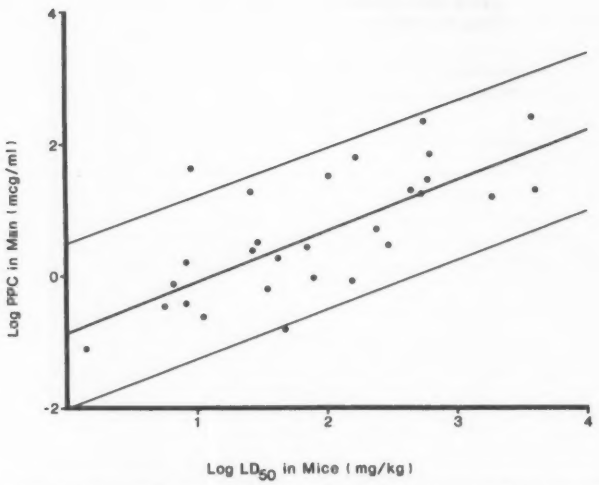

FIGURE 1.—Log-log multiple linear regression model that might prove useful to estimate the magnitude of clinically achievable PPCs in man for investigational compounds with known LD50 values in mice. The sample points within the (90%) confidence belts plotted on either side of the regression line represent the known data pairs of 28 anticancer drugs.

A linear regression analysis of log (PPC) on log (LD50) was performed to predict PPC in man based on the toxicity data from mice. Confidence intervals for predicting log (PPC) for new investigational drugs were computed using the following formula of the standard error (4):

$$S\hat{y} = Sy.x \sqrt{1 + 1/N + (x-\bar{x})^2/(N-1)Sx^2},$$

where $\hat{y}$ = predicted log (PPC) of new drug; x = log (LD50) of new drug; N = No. of drugs in the analysis; Sy.x = error of estimate; $\bar{x}$ = sample mean of log (LD50); and Sx^2 = sample variance of log (LD50).

RESULTS

The basic data for the 28 compounds used in this analysis are shown in table 1. The LD50s ranged from 1.4 to 4000 mg/kg while the PPCs ranged from 0.08 to 250 μg/ml. The relative closeness of the relationship between the logarithm of the doses determined to have major acute toxicity in mice (LD50) and that of clinically achievable PPCs in man (Pearson test) is indicated in figure 1 ($r^2 = 0.501$; $P < 0.0001$). The two lines plotted on either side of the regression line represent the 90% confidence interval for predicting log (PPC) for investigational compounds with selective information in terms of the LD50 in mice. The corresponding regression equation was defined as:

$$\log (PPC) = -0.788 + (0.755 \times \log (LD_{50})).$$

The standard errors for the intercept and slope were 0.314 and 0.148, respectively.

Since there was some suggestion that the variation in both log (LD50) and log (PPC) might in part be accounted for by the class of anticancer agent, we considered it necessary to control for the separate influence of this parameter (and thus exclude the possibility that the entire correlation can be explained solely by differences between different classes of agents): an analysis of covariance revealed that the type of agent was directly involved ($P < 0.05$); however, there was still a significant residual relationship between log (LD50) and log (PPC) ($P < 0.02$).

To evaluate the reliability of predicted drug levels and to determine whether the type of agent would have an impact on the predictive ability of the proposed statistical model, the deviation from observed to predicted PPC was calculated on a log basis for each compound and each class of cytotoxic compounds. These data are summarized in table 2. In general, the predictions of the PPC in man were reasonably good for individual compounds. Predictions deviated from observed values by > 1 log for only four of 28 drugs (thiotepa, menogaril, hydroxyurea, and ifosfamide). In all four drugs this divergency could not be related to any particular biological explanation. The overall deviation of a predicted value of log concentration in man was 0.69. Although the various classes of anticancer agents were represented by only a relatively small number of drugs, there was some suggestion that the PPC of antimetabolites tended to be underestimated by the model (mean deviation of predicted and observed PPC = −0.579), whereas the concentration of antitumor antibiotics was slightly overestimated (mean deviation = +0.484), a finding consistent with correlative data in terms of drug toxicity in mice and maximum tolerated dose in man (1).

DISCUSSION

The consideration of clinically valid and achievable plasma concentrations represents an important aspect when analyzing results of in vitro chemosensitivity

TABLE 2.—Deviation from observed to predicted PPC in man for several individual cytotoxic drugs and classes of agents

Agent	Deviation*
Alkylating agents	
Busulfan	+0.968
Carmustine	+0.144
Chlorambucil	+0.613
Cisplatin	−0.105
Cyclophosphamide	−0.152
Melphalan	−0.206
Thiotepa	−1.006
Mean	+0.256†
Antitumor antibiotics	
Dactinomycin	+0.419
Bleomycin	+0.609
Bisantrene	+0.318
Daunorubicin	+0.305
Doxorubicin	+0.601
Menogaril	+1.271
Mitomycin	−0.262
Mitoxantrone	+0.608
Mean	+3.869†
Antimetabolites	
Cytarabine	−0.490
5-Fluorouracil	−0.879
Floxuridine	−0.531
Hydroxyurea	−1.747
6-Mercaptopurine	+0.011
Methotrexate	+0.162
Mean	−3.474†
Plant alkaloids	
Etoposide	−0.795
Vinblastine	−0.051
Vincristine	+0.221
Mean	−0.625†
Miscellaneous	
Dacarbazine	+0.505
Hexamethylmelamine	−0.100
Ifosfamide	−1.055
PALA	+0.623

*Values are indicated on a log base: a + indicates that the real PPC value is lower than the estimate, and a − sign indicates that the estimate is lower than the real PPC value.

†Mean ± SD between observed and predicted PPC for the corresponding class of agent.

assays (5,6). Because this specific pharmacokinetic information is not available for most investigational anticancer chemotherapeutic drugs, it is difficult to interpret in vitro drug sensitivity data with respect to their relevance to clinical effectiveness.

Based on previous observations of a quantitative relationship between toxic doses in animal and man (1,2), we developed a statistical regression model that provided a reasonably good prediction of achievable PPCs in man based on LD50 values observed in mice.

The model predicted the peak plasma level to within 1 log, with 90% confidence for 26 of 28 drugs evaluated. While this model may not represent an optimal approach, it seems acceptable considering the overall reproducibility and reliability of the animal toxicology data (7). In addition, since there exists a considerable variation in PPCs achievable in man for the various agents (covering 4 logs, table 1), even a rough approximation of real values might be helpful in classifying drugs more accurately by their therapeutic value, rather than by their antiproliferative potency as with a comparison of various drugs on the basis of ID50 or ID90 values. In fact, when compounds are ranked only in terms of their ID50 or ID90 values, one only obtains a ranking in terms of potency which in itself is meaningless if not analyzed in the context of whether this dose will be an achievable PPC (which can be limited by toxicity). Use of the LD50 values in the current context provides predictive correction for toxicity based on the initial preclinical toxicology data in mice.

Since the number of compounds that had been included in our investigation was relatively small, and since the analysis of the log (LD50):log (PPC) relationship had been performed in a retrospective manner, the potential usefulness of the proposed statistical model for estimating PPCs of investigational compounds has to be considered critically. Based on the observation, however, that the class of anticancer agent is directly involved in the relationship between log (LD50) and log (PPC), collection of additional correlative drug data might ultimately lead to the development of an improved model giving more accurate and safer estimates, particularly if a new agent of a certain class is being tested.

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Study of Cardiovascular Autonomic Insufficiency in Advanced Cancer Patients[1]

E. Bruera,* S. Chadwick, R. Fox, J. Hanson, and N. MacDonald[2,3]

To determine the incidence of cardiovascular autonomic insufficiency (CAI), 43 patients with advanced breast cancer and 20 normal controls were evaluated using electrocardiographic tests (heart rate variation during deep breathing and Valsalva maneuver and upon standing) and clinical tests (blood pressure variation during hand grip tests and upon standing). Nutritional status, tumor mass, Karnofsky performance status (PS) score (0–100), and peripheral reflexes were also determined. Tests for CAI were abnormal in 43 patients (52%), versus seven of 100 in 20 controls (7%, $P < 0.001$). In cancer patients, tests for CAI were more frequently abnormal in patients with PS < 60 ($P < 0.01$), basal heart rate > 100 ($P = 0.05$), and malnutrition ($P < 0.01$). We conclude that CAI is a frequent finding in patients with advanced breast cancer and should be suspected mainly in patients with a low PS, tachycardia, or malnutrition. It is probably a multifactorial syndrome, and malnutrition, drugs, decreased activity, or paraneoplastic syndromes are all possible causes for CAI. [Cancer Treat Rep 70:1383–1387, 1986]

Autonomic insufficiency is a clinical syndrome including cardiovascular manifestations (postural hypotension, syncope, and fixed heart rate) and gastrointestinal symptoms [nausea, anorexia, constipation, or diarrhea (1–4)]. This syndrome has been found most commonly in neurologic disorders, chronic renal disease, and diabetes mellitus (1). There have been isolated reports suggesting the presence of autonomic insufficiency in advanced cancer patients (5–7).

The purpose of the present study was to determine the incidence of cardiovascular autonomic insufficiency (CAI) in a group of patients with advanced breast cancer, and to study its association with nutritional status, tumor mass, antineoplastic treatment, and basal heart rate and blood pressure.

PATIENTS AND METHODS

Between January and May 1985, 43 consecutive patients with advanced breast cancer (defined as either locally recurrent or metastatic disease) and 20 healthy adult controls were admitted to the study. No patient had a previous diagnosis of diabetes, renal failure, arterial hypertension, mediastinal or cardiovascular disease. Patients were not included in the study if they were taking any of the following drugs: diuretics, antihypertensive or antiarrhythmic drugs, digoxin, (anticholinergics, cholinergics), beta-blockers, or adrenergic stimulants. Seven patients (16%) were receiving narcotic analgesics. All patients had a normal baseline ECG. Characteristics of patients and controls are summarized in table 1. Patients who entered the study were admitted (15, 35%) or seen as outpatients at the Cross Cancer Institute (28, 65%). They were accrued consecutively if they met criteria for eligibility.

After informed written consent was obtained, the following evaluations were performed.

Autonomic neuropathy was assessed by clinical and electrocardiographic tests standardized in the investigation of diabetic autonomic neuropathy (2).

(*a*) Blood pressure changes on standing were measured at the brachial artery with a sphygmomanometer. Failure to increase systolic pressure was scored as a pathological response.

(*b*) Diastolic pressure modifications during handgrip were tested. Pressure rises of < 5 mm Hg were counted as abnormal. (Patients were asked to squeeze a blood pressure cuff at 30% of their maximal strength.)

ECG tests were as follows.

(*a*) Beat-to-beat (R-R interval) heart rate variation was assessed during a Valsalva maneuver. The ratio of the longest R-R interval during release

[1] Received Nov 12, 1985; revised July 14, 1986; accepted Aug 1, 1986.

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[3] We thank Liz Berglind and Karen Vance for their assistance in the preparation of this manuscript.

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TABLE 1.—Characteristics of patients and controls

Characteristic	Patients ($n = 43$)	Controls ($n = 20$)
Age (mean ± SD)	56 ± 10	50 ± 9*
Females/males	42/1	14/6
No. of admitted patients/outpatients	15/28	—

*$P < 0.01$.

to the shortest R-R interval during strain was calculated. Ratios of < 1.10 were recorded as abnormal.

(*b*) Heart rate changes during deep breathing in the supine position (at six breaths/minute) were studied. Rate variations of < 10 beats/minute were considered pathological.

(*c*) Continuous ECG recording was performed on standing from a reclining position. R-R intervals at beats 15 and 30 after standing were measured to give the 30/15 ratio. Ratios of ≤ 1.00 were interpreted as abnormal.

Nutritional status was determined by four measurements: actual/usual weight index, triceps skinfold, arm muscle circumference, and serum albumin. All the measurements were performed as suggested by Blackburn and Thornton (8), and were expressed as a percentage of the standard value for each test. The four resulting percentages were averaged; when the final average was ≥ 85, the patient was considered normally nourished, and when it was < 85, the patient was considered malnourished. Weight was not employed in the nutritional evaluation when usual weight could not be obtained (two cases), or when the patient had any evidence of fluid retention (three cases). This method has been previously employed by our group (9,10).

Tumor mass was estimated according to the following score (9): 0 = no lesions; 1 = one lesion < 5 cm in any diameter; 2 = one lesion > 5 cm in any diameter or up to two lesions; 3 = between three and five lesions; 4 = > five lesions. The estimation was performed by reviewing the patient's clinical history and considering all physical and radiological findings reported in the chart.

Neurological examination was performed in all cases to establish the status of peripheral reflexes.

Karnofsky index was used for the determination of performance status (PS) (11).

Statistical Analysis

Statistical analysis was performed using the "Statistical Package for the Social Sciences" (12). The "z" test was used for the comparison of proportions and the "t" test for the comparison of means. To test for differences in abnormalities according to the presence or absence of different factors (table 2), the proportion of abnormal tests (some cases did not have all tests performed) was calculated for each patient, and the Wilcoxon rank sum "w" test was used to compare the groups defined by the different variables.

RESULTS

A total of 21 tests (9%) were not performed in the 43 breast cancer patients. Heart rate and blood pressure variation upon standing could not be performed in eight cases because of the inability of the patient to stand up readily; blood pressure variation during handgrips and

TABLE 2.—Incidence of abnormal tests for CAI, according to difference variables*

Variable	Presence of variable		Absence of variable		
	No. of patients	Mean rank	No. of patients	Mean rank	*P* value
Radiation to the left hemithorax†	22	21.1	20	22	NS‡
Chemotherapy including vinca alkaloids	22	21.7	21	22.3	NS
Abnormal reflexes†	2	18.6	35	25.3	NS
Tumor mass§ Grade III-IV	34	21	6	17.8	NS
Karnofsky PS score < 60	11	31.5	32	18.7	< 0.01
Basal heart rate¶ ≥ 100	10	28	32	19.5	0.05
Malnutrition ≤ 85%	8	32.2	35	19.7	< 0.01

*Patients were ranked according to the proportion of abnormal tests for CAI and the mean rank for each group was calculated.

†6 patients were not evaluable.

‡NS = not significant.

§3 patients were not evaluable.

¶1 patient was not evaluable.

TABLE 3.—Incidence of abnormal tests for CAI in patients and controls*

	Patients	Controls	*P* value
Heart rate Slow, deep breathing (6 × min)	15/43 (35)	1/20 (5)	< 0.01
Heart rate Valsalva maneuver	24/43 (56)	1/20 (5)	< 0.01
Heart rate Standing	18/35 (51)	0/20 (0)	< 0.01
Blood pressure Handgrip maneuver	23/40 (57)	2/20 (10)	< 0.01
Blood pressure Standing	20/33 (61)	3/20 (15)	< 0.01
Totals	100/194 (52)	7/100 (7)	< 0.001

*Data are expressed as: abnormal tests/tests performed (%).

upon standing could not be performed in two cases because of bilateral arm swelling, and blood pressure during handgrip was not performed in one case because of protocol violation. The results after the performance of the 326 evaluable tests for CAI, as well as the results after the evaluation of nutritional status, are summarized in table 3 for patients and controls. Eighteen of 43 patients (42%) had at least three abnormal tests for CAI, versus zero of 20 controls (0%, $P < 0.001$). Six of 43 patients (13%) had abnormal results in all the tests for CAI.

The association between abnormal tests for CAI and nutritional status, tumor mass, blood pressure, and heart rate are summarized in Table 2. Age, sex, and baseline arterial blood pressure showed no significant association with tests for CAI.

Clinical symptoms of postural hypotension (vertigo, blurred vision, or light-headedness upon standing), or chronic unexplained nausea (lasting > 3 weeks) were reported by four of six (67%) and three of six (50%) patients with 100% abnormal tests for CAI, respectively, versus two of 37 (5.4%, $P < 0.01$) and four of 37 (10%, $P < 0.05$) in patients with < 100% abnormal tests for CAI, respectively.

Three patients with four of five, five of five, and five of five abnormal tests for CAI, respectively, showed significantly prolonged gastric emptying time when studied by radionuclide scan (gastric emptying times of 300, 180, and 240 minutes, respectively, versus a normal of 70 minutes in our control population).

The results of tests assessing mainly parasympathetic function (Valsalva maneuver and heart rate while breathing) did not differ significantly from those of tests assessing mainly sympathetic function (handgrip and blood pressure while standing up).

The combination of heart rate > 100/minute and a PS score of < 60 could predict the presence of > 75% of abnormal tests for CAI in 75% of the cases.

The incidence of abnormal tests for CAI was 16 of 28 (56%) in seven patients receiving narcotic analgesics, versus 84 of 166 in patients not receiving narcotics (52%, P = NS).

DISCUSSION

Cancer patients frequently present symptoms such as anorexia, nausea and vomiting, constipation, or postural hypotension. All these symptoms can be influenced by the autonomic nervous system. A better knowledge of the status of autonomic function in this population might help to explain some of these symptoms and might contribute to their better pharmacologic management.

Though isolated case reports have suggested the presence of autonomic insufficiency in advanced cancer (5–7), there are no studies defining the incidence of this abnormality. Our study demonstrates a significantly higher incidence of abnormal tests for CAI in patients with advanced breast cancer, as compared to normal controls. The reliability of the methods we used for the study of CAI is suggested by the fact that the results were consistently normal in the control group (table 2), and also because they have previously been used extensively in different conditions associated with autonomic neuropathy (1–3,6,15). Though our controls were slightly younger than our patients, age has not been found to be related with abnormal tests for CAI (1–3), and in our patients, age could not be correlated with abnormal tests for CAI.

In cancer patients, the presence of abnormal tests was significantly associated with tachycardia, malnutrition, and a low PS score.

A recent review suggested malnutrition as one of the possible causes of autonomic insufficiency (1). Elegant studies on animals have suggested that fasting suppresses the activity of the sympathetic nervous system (13). Studies carried out by Jewish physicians in the Warsaw ghetto during World War II showed that victims of starvation demonstrated bradycardia, low arterial blood pressure, and absence of increase in pulse rate or arterial blood pressure after a work stimulus (14). Though

malnutrition was associated with a higher incidence of abnormal tests for CAI, there was also a significant percentage of abnormal tests for CAI in patients without malnutrition (table 2).

The association between CAI and tachycardia probably just reflects the fact that unexplained tachycardia is considered one of the features of CAI by some authors (2,3).

Though morphine (15) and tricyclic antidepressants (16) have been found to cause autonomic changes, our results suggest that they were not major factors influencing the incidence of CAI.

The association between abnormal tests for CAI and PS score is probably reflecting the correlation found between PS and malnutrition ($r = 0.52$, $P < 0.001$). However, this may also mean that patients with lower PS (bedridden, in wheelchair, or with subclinical dehydration) might develop autonomic disturbances. Patients with advanced cancer who spend much of the day in bed might have a "deconditioning" effect on autonomic functions. This effect might be unrelated to the tumor, and might be shared with other disabling diseases. This point should be addressed in further research.

A previous study by our group suggested that there is an increased percentage of abnormal tests for CAI in patients receiving vinca alkaloids (17). Only 22 of our patients had received vinca alkaloids, and the total dose received was very low (average, 1.5 courses of chemotherapy including vinca alkaloids); the three patients who had received the highest dose of vinca alkaloids had 12 of 13 (92%) abnormal tests.

There are two clinical reports suggesting that CAI might be a paraneoplastic manifestation of advanced cancer. Park et al (7) reported a patient with bronchial carcinoma who had postural hypotension and abnormal tests for CAI that disappeared after irradiation of the tumor. In the second report (6), a patient developed intestinal pseudo-obstruction and abnormal tests for CAI; after her death an autopsy demonstrated degeneration of autonomic nerves without tumor involvement in the area.

The clinical consequences of our findings are likely to be similar to those already demonstrated for diabetic patients, in whom the most frequent clinical manifestations of CAI are postural hypotension and resting tachycardia. These findings are frequently noted in advanced cancer patients. In addition, patients with diabetic autonomic neuropathy and primary dysautonomic syndrome frequently show symptoms ascribed to gastric paresis, mostly chronic nausea, anorexia, and early satiety (18). All of these features are frequently present in advanced cancer patients (9,19). One recent report suggests gastroparesis as a complication of advanced cancer (20). Three of our patients with four of five, five of five, and five of five abnormal tests for CAI, respectively, complained of chronic unexplained nausea, and a radionuclide scan showed a significantly prolonged gastric emptying time (190, 320, and 200 minutes, respectively, versus a normal of 70 minutes in our control population). Barium meal and gastroscopy failed to demonstrate mechanical obstruction in the three cases. Finally, at autopsy the immediate cause of death could not be explained in 4.4%–23% of cancer patients (21–24). CAI has been associated with a high incidence of sudden death in diabetics (2,3,25) and might be the contributing cause of some of these unexplained deaths in patients with advanced cancer.

Our findings suggest that CAI is a frequent feature in advanced cancer, and should be suspected mainly in patients with unexplained tachycardia, low performance status, and malnutrition. It is probably a multifactorial syndrome, and malnutrition, decreased activity, drugs (vinca alkaloids, narcotics, and tricyclics), or paraneoplastic syndromes are all possible causes for CAI.

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Final Report of the Phase I Trial of Single-Dose WR-2721 [*S*-2-(3-Aminopropylamino)ethylphosphorothioic Acid][1,2]

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Two hundred one patients were entered in a single-dose phase I trial of WR-2721 [*S*-2-(3-aminopropylamino)ethylphosphorothioic acid]. Major toxic effects included emesis and hypotension. The observed minor toxic effects were somnolence and sneezing. Two infusion schedules were tested: (*a*) *long-infusion time,* which fixed the rate, but varied total time; and (*b*) *short-infusion time,* which varied the rate, but fixed the time to 15 minutes. Emesis was significantly influenced by infusion time; the long schedule caused a 57% incidence whereas the short schedule caused only a 28% incidence. Within the long-infusion group, higher-dose patients and women were more likely to vomit. Although only 15% of the entire group had hypotension, the long-infusion schedule had a hypotension incidence of 23%; the short schedule had an incidence of only 3% ($P < 0.0005$). Within the long-infusion group, dose and tumor site significantly influenced the incidence of hypotension. No factors were associated with these toxic effects in the short-infusion schedule. However, certain toxic effects were too infrequent to detect significant differences. For future trials we recommend 740 mg/m^2 infused in 15 minutes. With this schedule, vomiting was seen in 25% of infusions and hypotension was seen in only one of 68 infusions. To date, no delayed toxic effects have been detected in any organ system, and the trial resulted in no toxic deaths. [Cancer Treat Rep 70:1389–1393, 1986]

WR-2721 [*S*-2-(3-aminopropylamino)ethylphosphorothioic acid] is a phosphorothioate which provides selective normal tissue protection to pretreated, tumor-bearing animals exposed to ionizing radiation and alkylating agents. The precise mechanism by which sulfhydryl compounds protect is not clear. Scavenging of free radicals and competition with oxygen by hydrogen donation to the free radicals, including the biologically critical molecules, are two frequently proposed hypotheses. Many sulfhydryl compounds have demonstrated protection from the effects of ionizing radiation plus alkylating agents and cisplatin. The distinctive properties of the amino-phosphorothioate compound WR-2721 in animal systems are its differential protection of normal tissues, as compared to tumors, and its relatively low toxicity. The phosphate covering the sulfhydryl group of WR-2721 reduces the toxicity of this drug, which requires dephosphorylation to become the active protector. There is evidence for active transport into normal tissues but only passive diffusion into tumors (1). However, other mechanisms, such as reduced supply of drug due to deficient vascularity (2,3), less protection of hypoxic (tumor) cells (4), and possibly membrane differences between normal tissue and tumor or less efficient metabolic conversion to active protector drug by tumor (5,6), have been proposed. Many experimental models have been tested, and dose reduction factors are generally quite small for tumors, as compared to those reported for normal tissues (7–9).

Human trials of WR-2721 with alternative formulations and schedules preceded this study. The US Army used an oral formulation. Thirty-six normal adult male volunteers received escalating doses from 100 mg to 5 g. The observed toxic effects were nausea and vomiting, abdominal cramps, and diarrhea (10). Using an iv formulation in Japan, Tanaka and Sugahara (11) treated 76 patients with 2.0 mg/kg/day (approximately 75–80 mg/m^2). Although the total number of treatments at this dose is not detailed, toxicity was minor with this daily dose. In

[1] Received Mar 21, 1985; revised July 14, 1986; accepted Aug 8, 1986.
[2] Supported in part by Public Health Service grants CA-30100, CA-16520, and CA-07153 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.
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the 76 patients, fever was the most common toxic effect (eight), followed by rash (seven), nausea (four), and diarrhea, vomiting, headache, and chills (one each). Thus, different formulations, routes of administration, and schedules produced different toxicity.

The purpose of this phase I study was to determine the toxicity and safety of escalating single doses of WR-2721. It was initiated at the University of New Mexico (12) and completed at the University of Pennsylvania.

MATERIALS AND METHODS

Two hundred one patients were entered in this trial with WR-2721 infused before treatment in 62 patients receiving radiotherapy and in 139 receiving chemotherapy. The median age was 59 years (range, 24–76). There were 121 males and 80 females. The group consisted of 150 Whites, 44 Blacks, four Hispanics, and three Orientals.

Patients in this study presented with malignancies which either had low expectation (< 10%) of cure or were refractory to standard therapy. All patients received either palliative radiotherapy or single-agent chemotherapy consisting of mechlorethamine, cyclophosphamide, or cisplatin 15–30 minutes after WR-2721 infusion. Prior to entry, all patients had a history and physical examination, cbc, serum chemistry battery (electrolytes, BUN, creatinine, alkaline phosphatase, acid phosphate, bilirubin, SGOT, SGPT, LDH, calcium, and phosphorus), and an electrocardiogram. Patients with abnormal renal or hepatic function were excluded. All patients had a minimal hemoglobin of 10 g/dl. Age was confined to those between 20 and 80 years. A life expectancy of at least 2 months was required. Prior antineoplastic treatment must have been completed at least 3 weeks before entry in the study. Vital signs were observed for 15–60 minutes immediately prior to infusion to establish a baseline range for blood pressure and pulse. Blood pressure readings were then obtained every 1–3 minutes during infusion, every 3–5 minutes after infusion for 1 hour, and then at least every 15 minutes for at least 4 hours. An episode of 20-torr drop in systolic blood pressure for 5 minutes at any time during observation defined hypotension regardless of symptoms. The initial 13 patients were treated with a drug synthesized at Walter Reed Army Institute of Research, Washington, DC; the drug was formulated by the East Tennessee Cancer Research Center, Knoxville. All other patients were treated with a drug supplied by the Pharmaceutical Resource Branch, Division of Cancer Treatment, Bethesda, MD. The drug was supplied in 500-mg vials and stored frozen. Immediately prior to infusion, the white crystalline powder was reconstituted with 9.5 ml of 5% dextrose and lactated Ringer's solution titrated to pH 7.2–7.3. The drug was stable at alkaline pH, but hydrolysis occurred rapidly in acid. WR-2721 toxicity was evaluated and recorded in these patients *before* the chemotherapy was administered.

A modified Fibonacci dose-search scheme provided dose levels tested. The escalation scheme called for levels at 50, 100, 170, 250, 340, 450, 600, 740, 910, 1100, and 1330 mg/m^2. Although the study allowed patients to receive subsequent doses, this report details toxicity for patients only during their first exposure to WR-2721.

Patients who manifested toxicity that required curtailing the intended dose are recorded by the dose actually administered before aborting the infusion. Because of the toxicity observed at 340 mg/m^2, the dose was reduced, and a new level at 300 mg/m^2 was created. Pretreatment with WR-2721 before radiotherapy was accomplished in three patients at each level before any patients receiving chemotherapy were entered. In patients who received chemotherapy, pretreatment doses with WR-2721 were started at 450 mg/m^2.

Infusion times varied and these changes in infusion time were sequential during the study. Doses between 25 and 300 mg/m^2 were infused in 5 minutes early in the study. Later, a constant rate of infusion schedule of roughly 14–20 mg/m^2/minute was introduced. A formula for infusion time was devised based on plasma volume calculated according to height, weight, and sex and assuming a plasma half-life of 4 minutes. Using this formula, infusion times were planned to limit the maximal WR-2721 plasma concentration to 65 mg/L. The infusion time varied from patient to patient between 5 and 120 minutes depending on total dose and surface area. One hundred twenty-eight patients were treated with this schedule, called the "long-infusion time" schedule. Subsequently, infusion time was fixed to 15 minutes, the "short-infusion time," and the dose was escalated again from 450 to 1100 mg/m^2.

Patients were followed with the same serial blood studies required for admission at Months 3, 6, and 12 from WR-2721 administration to evaluate for delayed toxicity to the hematopoietic, hepatic, and renal systems.

Data analysis used the chi-square test with the Yates correction if appropriate, the Fisher exact test, the t test, or the Wilcoxon rank-sum test. Infrequent categories were combined if necessary for the test and if medically meaningful.

RESULTS

Tables 1 and 2 separate the patients into two groups which are divided by method of infusion. The major toxic effects are emesis and hypotension; the minor toxic effects are somnolence and sneezing. Observations of hypocalcemia have been reported (13). Studies to detect calcium fluxes were not done in this group. In this analysis, we evaluated the influence of age, race, sex, primary tumor site, dose, and infusion time in relation to these toxic effects.

To eliminate the potential confounding effect of infusion time, the patients were grouped into long-infusion time (table 1) and short-infusion time (table 2).

Emesis

The frequency of emesis in the long-infusion schedule was 57% (70 of 122 patients) (table 1). In the short-infusion schedule, the incidence of emesis was 28% (22 of

TABLE 1.—Dose levels and frequency of WR-2721 toxicity: long-infusion time

Dose (mg/m^2)	No. of patients	Toxic effect			
		Emesis	Hypotension	Somnolence	Sneezing
50–170	8	0	0	0	0
250	5	3	0	0	0
300	3	3	1	0	0
340	6	1	2	0	0
450	32	16	1	7	6
600	8	4	2	3	0
740	30	20	12	10	8
910	16	11	6	4	0
1100	7	6	1	2	2
1330	7	6	3	5	4
	122	70 (57%)	28 (23%)	31 (25%)	20 (16%)

79) (table 2). This difference was significant ($P < 0.005$). Within the long-infusion set of patients, two other significant observations were found. Patients who vomited received higher doses than those who did not ($P = 0.0003$). Women experienced emesis in 70% of long infusions, and men experienced emesis in 49% of long infusions. This difference was significant ($P = 0.031$), while the distributions of dose for men and women were similar ($P = 0.45$). Disease site (table 3) and race did not influence the frequency of emesis in either the long- or short-infusion schedule. Within the short-infusion group, patients who vomited received higher doses than those who did not ($P = 0.011$).

Hypotension

In the entire group, 30 of 201 patients (15%) had hypotension. Twenty-eight of 122 patients (23%) had hypotension with the long-infusion schedule but only two of 79 patients (3%) experienced hypotension with the short-infusion schedule. The influence of infusion time was significant ($P < 0.0005$). Within the long-infusion group, patients with hypotension received higher doses than those without hypotension ($P = 0.002$). Within the short-infusion group, with only two hypotensive patients (740 mg/m^2), one could not draw an inference regarding the effect of dose. Table 3 divides the group into the long and the short schedule and reports the frequency of hypotension for each tumor site. In the long schedule tumor site significantly influenced hypotension ($P < 0.001$). Hypotension clusters appeared in two disease sites: head and neck (50%) and lung (38%). The dosages for these head and neck and lung groups were similar to dosages for the other long-schedule patients ($P = 0.23$). A detailed review of the lung and head and neck groups failed to find the following: lower performance status, poorer hydration status, medications, premorbid diseases, or chemotherapy or radiotherapy grouping or clustering in any dose category. No effect of tumor site was seen when the short-infusion schedule was used; however, only 15 head and neck and lung patients were treated by the short schedule. Furthermore, in the short-infusion time group, hypotension was seen in 17% of the Black/Oriental subset, but in none of the Whites, which was a significant observation ($P = 0.017$).

Minor Toxic Effects

Significant observations have been found for somnolence with long-infusion schedules. Dose significantly altered occurrences of somnolence. The group showing somnolence received higher doses than the group without somnolence ($P = 0.001$). Sex also influenced the incidence of somnolence. Women became sleepy during infusion in 36% of the group, but men experienced sleepiness in only 18% ($P = 0.0046$). As noted above, the distribution of dose for men and women was similar. Similarly, nonwhites experienced somnolence in 41% of infusions as opposed to whites, who were sleepy during 18% of the infusions ($P = 0.013$). Sneezing was also related to higher doses in the long schedule ($P = 0.024$).

TABLE 2.—Dose levels and frequency of WR-2721 toxicity: short-infusion time

Dose (mg/m^2)	No. of patients	Toxic effect			
		Emesis	Hypotension	Somnolence	Sneezing
450	7	1	0	2	2
740	68	17	1	3	18
910	2	2	0	1	0
1100	2	2	1	2	0
	79	22 (28%)	2 (3%)	8 (10%)	20 (25%)

TABLE 3.—Tumor site and incidence of WR-2721 toxicity

Site	Short-infusion time			Long-infusion time		
	No. of patients	Emesis	Hypotension	No. of patients	Emesis	Hypotension
Bone	3	2	1	8	5	1
Esophagus	7	1	0	5	2	1
Head and neck	7	1	0	16	8	8
Lung	8	3	1	32	19	12
Melanoma	23	8	0	1	1	1
Other	1	0	0	6	3	3
Gastrointestinal	25	5	0	33	20	2
Genitourinary	2	0	0	16	9	0
Sarcoma	3	2	0	5	3	0
	79	22	2	122	70	28

Subsequent Treatment

Seventy-six of the 201 patients had subsequent courses of WR-2721. An interval of at least 3 weeks elapsed prior to a second course. Of these 76 patients who had no toxicity during the first course, 17 manifested emesis or hypotension during subsequent courses. Among these 17 patients, three had major problems with hypotension causing cessation of intended total dose.

DISCUSSION

This analysis establishes dose, infusion time, and the tumor sites (lung and head and neck primaries) as important variables in the major toxicity of the protector WR-2721. While the relationship between infusion time and dose and emesis was previously suggested (14), this report puts this assertion on firm statistical ground. More important, this report establishes significant relationships between hypotension and (*a*) the long-infusion time, (*b*) the dose within the long-infusion time, and (*c*) the primary tumor sites in the head and neck region and lung.

In regard to minor toxic effects we found somnolence in the long-infusion time to be significantly influenced by sex and race. Women became somnolent in 30% of infusions, as opposed to men, who experienced somnolence in 18% of infusions. Forty-one percent of the Black/Oriental subset had somnolence, but only 18% of the Whites experienced somnolence.

The evolution of the infusion schedules warrants explanation. When substantial incidence of emesis occurred at a dose believed to be suboptimal for protection (340 mg/m^2), infusion time was lengthened to avoid a putative threshold toxic dose. When infusion times exceeded 1 hour, two prospects were considered. First, although it was hoped to avoid the toxic threshold level, a plasma at higher peak level might be needed to drive drug into cells. Second, animal pharmacokinetics suggested a closing of the gap between normal tissue concentrations and tumor concentrations of WR-2721 as infusion times approached 1 hour. To address these points, two schedules were tested. In one group, the infusion time was fixed at the rate used for 1100 mg/m^2 (approximately 1 hour) and the dose escalated to 1330 mg/m^2. In the second group, the infusion time was fixed at 15 minutes and the dose was escalated from 450 to 1100 mg/m^2. The patients entered on the short and long schedules had similar performance status, and criteria for study inclusion did not change. If anything, the bias we held was that the longer infusions would be better tolerated than the shorter.

Toxicity increased both in frequency and in severity at doses $>$ 740 mg/m^2. When emesis induced by WR-2721 occurred, it was not readily controlled with standard antiemetics such as dexamethasone, prochlorperazine, or metaclopramide. Most hypotension was asymptomatic. Symptomatic hypotension has been quickly reversed by Trendelenburg position or infrequently by volume expansion.

The concept of maximum tolerated dose is useful in cytotoxic therapy. In drugs intended to modify toxicity, like WR-2721, this concept is less helpful. The fundamental issue is finding the least toxic dose that enables protection, as opposed to pushing the dose to tolerable toxicity, which is the principle used with cytotoxic drug investigation. The dose of 740 mg/m^2 infused in 15 minutes caused emesis in about 25% of 68 patients and hypotension occurred in only one. This dose has tolerable adverse effects and is the recommended dose for phase II studies.

Safety with subsequent doses is less well established. The lack of toxicity on first exposure failed to predict the side effects in subsequent doses in 17 of 76 patients who agreed to another trial. Because these are selected patients, this may represent an underestimate of the toxicity that subsequent infusions may cause. On the other hand, serial chemistry evaluations of liver and renal function, hemoglobin, hematocrit, and wbc and platelet counts detected no delayed organ toxicity. There were no toxic deaths.

Two iv formulations were used in this single-dose study. When others used an oral formulation (10), abdominal cramps and diarrhea were common, but we found none with the iv formulations. The report from Japan (11) used a daily iv schedule and their own for-

mulation. Although the most frequent toxic effect seen in Japan is fever, there are no cases of fever with single doses.

The explanation may be that multiple doses are required to produce fever or that some formulations or lots may contain pyrogens. The doses and schedules were also different between this study and those reported previously. We noted no difference between the two formulations used; however, the Walter Reed formulation was used with the lowest dose levels.

A reliable pharmacokinetic assay (15) was not available until this study was nearly complete. Data on plasma clearance of WR-2721 in animals and man using a rapid bolus of 150 mg/m^2 are available, and tissue assays of WR-2721 and WR-1065 (the dephosphorylated compound thought to be the active protector) are being investigated (16-18).

CONCLUSIONS

The results of this study show the following.

1. Infusion of 740 mg/m^2 in 15 minutes is the recommended dose for subsequent trials.
2. Principal toxic effects are emesis and hypotension.
3. Patients with the primary tumor sites of head and neck and lung exhibited a significant proportion of hypotension.
4. No delayed organ toxicity or death has been detected.
5. Human pharmacokinetics and phase II studies preceding both chemotherapy and radiotherapy are under way.

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Combined Alkylators and Multiple-Site Irradiation for Extensive Small Cell Lung Cancer: A Southwest Oncology Group Study[1,2]

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The Southwest Oncology Group performed a study for patients with extensive small cell lung cancer in which two hypotheses were tested: (*a*) that combined alkylating agents for induction might improve the initial response rate; and (*b*) that multiple-site, involved-field consolidation with irradiation in patients with response to chemotherapy might further improve response quality and duration. A regimen of combined alkylating agents plus vincristine [carmustine, thiotepa, vincristine, and cyclophosphamide (BTOC)] was compared to our standard program of cyclophosphamide, doxorubicin, and vincristine (CAV). Patients with bone marrow metastases and/or disseminated bone metastases were randomized to BTOC or CAV as initial induction therapy, but received no multiple-field irradiation afterward. Among 189 such patients, the overall response rates were similar (48% to BTOC and 61% to CAV, with complete remission in 5% and 15%, respectively). Toxic effects were also comparable, with 23% sustaining life-threatening or fatal complications on BTOC and 16% on CAV. Median survival (5.9 and 7 months for BTOC and CAV, respectively) and overall survival were not different, and are superimposable upon our previously reported results with CAV alone. For patients with no evidence of bone marrow involvement and no metastases identified beyond the confines of ipsilateral hemithorax, liver, and brain, the plan of therapy consisted of induction chemotherapy (BTOC or CAV) every 3 weeks for three cycles, followed by multiple-field irradiation consolidation to sites of prior involvement. Among 239 such patients, response rates to therapy initiated with BTOC and CAV were also similar: 54% for BTOC and 62% for CAV, with complete response in 16% and 13%, respectively. However, the program of BTOC followed by multiple-site irradiation was associated with a higher incidence of severe or life-threatening thrombocytopenia (23% versus 8% for CAV), accounted for almost entirely by patients receiving hepatic irradiation after chemotherapy, among whom the incidence of this complication (grade 3 or 4) was 76% and 14%, respectively. Other toxic effects, including granulocytopenia, were comparable. With the exception of thrombocytopenia in the cited subgroup, multiple-field irradiation consolidation proved feasible and tolerable, with improved quality of response evident after its initiation in 24% of 135 patients. However, a similar proportion developed disease progression during or shortly after radiation therapy, and the median survival of patients who received irradiation was only 9 months (7 months from the start of consolidation). Neither combined alkylating agents at doses equitoxic to CAV nor the use of multiple-site, involved-field irradiation as a consolidation measure can be recommended, based on the outcome of this study. [Cancer Treat Rep 70:1395-1401, 1986]

[1] Received Apr 21, 1986; revised Aug 12, 1986; accepted Aug 19, 1986.

[2] Supported in part by Public Health Service grants CA-20319, CA-22433, CA-13238, CA-12644, CA-22433, CA-20319, CA-04919, CA-04920, CA-03389, CA-32734, CA-27057, CA-37981, CA-14028, CA-03096, CA-21116, CA-22411, CA-35128, CA-16385, CA-35995, CA-36020, CA-35117, CA-35274, CA-04915, CA-35996, CA-12213, CA-35438, CA-03392, CA-35261, CA-35090, CA-35176, CA-35281, CA-35192, CA-35158, CA-35226, CA-35431, CA-35200, CA-37445, CA-13612, CA-35109, CA-35262, CA-35440, CA-28862, and CA-32102 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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It is known that there are different sites of covalent modification of DNA by the compounds classified as alkylating agents (1), as well as differences in mechanisms of transport and activation. That these differences may be important is supported by an impressive body of experimental data from preclinical systems, reviewed by Schabel et al (2,3). In summary, these data show that the toxicity of alkylating agent combinations is usually subadditive, and that therapeutic synergism exists, both for combinations of standard agents with different alkylating moieties (eg, cyclophosphamide and melphalan) and for combinations with nitrosoureas in a broad spectrum of murine leukemias and solid tumors, provided that peak blood levels of each agent are present at the same time. Further, sublines of L1210 leukemia selected for resistance to one alkylator often retain some sensitivity to other classical alkylators and full sensitivity to the nitrosoureas. Based on these considerations, we decided to test a combination of alkylating agents from each of three different chemical groups in the treatment of extensive small cell lung cancer. Cyclophosphamide was chosen as the mustard, carmustine as the nitrosourea, and triethylenethiophosphoramide (thiotepa) as the ethylenimine, based on extensive clinical experience with each of these agents and on its availability in parenteral form. Because of evidence from a prospective, controlled trial that vincristine added to a cyclophosphamide-nitrosourea-based combination improved both response duration and survival (10), we gave this agent as well, producing a four-drug combination (BTOC) which was initially piloted at the Cleveland Clinic. Our intention in the groupwide study reported here was to prospectively compare the BTOC combination to our standard regimen of cyclophosphamide, doxorubicin, and vincristine (CAV).

A second goal of this study was to assess the potential value of multiple-field, local irradiation consolidation, when feasible, to all sites of known prior disease involvement in responding patients. This was stimulated by an analysis of sites of failure in our previous groupwide study involving CAV chemotherapy with chest and brain radiotherapy in responders (4) (R. B. Livingston, unpublished data). In that study, among 36 patients with known prior hepatic involvement who relapsed, 12 (33%) had initial failure clinically confined to the liver and five more failed in the chest and liver simultaneously without clinical involvement of other sites. Among 12 with known prior brain metastases who relapsed, four relapsed in the brain without other apparent sites of failure, and three others failed in the chest and brain only. Half the patients entered on our prior study had liver or brain involvement, and half of these had only one clinically evident systemic site. Thus, if further reduction of residual tumor in the liver and brain could be obtained among patients who responded to initial chemotherapy, we reasoned that a substantial proportion might benefit. We hoped to accomplish this using radiation therapy as a non-cross-resistant modality in sequence after induction with BTOC and CAV. Patients with brain metastases would receive a higher dose to the whole brain than we had employed previously and a boost to bulk disease; those with liver metastases would receive whole-liver irradiation to a dose that might control microscopic disease, with a similar boost option; and the primary tumor would be treated with definitive rather than palliative intent, in a split-course fashion so that patients with hepatic involvement would receive radiation therapy to the site during the rest period for chest fields. We decided to attempt radiation consolidation only in patients whose known sites of prior disease involvement could be encompassed by the planned treatment fields. Because of evidence that cisplatin plus etoposide was a very effective and potentially non-cross-resistant drug combination for small cell lung cancer (5), and evidence of benefit from reinduction chemotherapy in a previous randomized trial by the Southwest Oncology Group (SWOG) (21), we chose to give these two agents as pulsed reinduction and late intensification. No maintenance chemotherapy was administered.

MATERIALS AND METHODS

The study was opened in March 1982, and closed to new patient entry in March 1985. Patients with extensive disease, defined as spread beyond the ipsilateral hemithorax and its regional nodal drainage, were considered eligible. Those with isolated pleural effusion or supraclavicular nodes were excluded and considered as having limited disease. Prior chemotherapy or radiation therapy was not permitted, and patients with uncontrolled congestive heart failure were not entered. There were no age restrictions or exclusions for abnormal hepatic or renal function, although dose modifications in chemotherapy were made as appropriate for the latter. Registration was through the SWOG Statistical Office. At the time of registration, patients were stratified as to performance status (PS) (fully ambulatory, PS 0–1, versus less than fully ambulatory, PS 2–4). In the absence of bone or bone marrow involvement, or if the bone involvement was confined to the areas specified for radiation therapy (chest and brain), patients were designated as belonging in *Group A* and their plan of treatment was with induction chemotherapy, followed by radiation therapy consolidation (table 1). If the bone marrow was found to be involved and/or bone metastases were identified in areas outside the planned radiation therapy fields, patients were placed in *Group B* and their plan of treatment was with randomized induction chemotherapy (BTOC versus CAV), followed by cisplatin and etoposide (table 2).

Definitions of complete and partial response, and of disease progression, were those of the SWOG as previously defined (21). Statistical analysis utilized the chi-square test with Yates' correction for comparison of response and toxicity rates, and the log-rank test (two-sided) for comparison of survival distributions. A P value of ≤ 0.05 was considered significant.

Patients who presented with brain metastasis in either

TABLE 1.—Treatment plan for Group A patients

Induction chemotherapy at Weeks 0, 3, and 6		
BTOC	vs	CAV
Carmustine, 100 mg/m^2 iv		Cyclophosphamide, 750 mg/m^2
Thiotepa, 20 mg/m^2 iv		Doxorubicin, 50 mg/m^2
Cyclophosphamide, 500 mg/m^2 iv		Vincristine, 2 mg
Vincristine, 2 mg		
↓		
Radiation therapy consolidation at Week 9		
Neck nodes	(if involved)	300 cGy × 13 = 3900 cGy total
Brain	(elective)	300 cGy × 10 = 3000 cGy total
Chest	(large field)	180 cGy × 10 = 1800 cGy total
↓		
Liver	(if involved)	170 cGy × 15 = 2550 cGy total
↓		
Chest	(reduced field)	250 cGy × 12 = 3000 cGy total
↓		
Reinduction chemotherapy at Week 18		
Etoposide, 60 mg/m^2/day × 5, iv		
Cisplatin, 60 mg/m^2, Day 5 only, iv		
↓		
Initial induction (CAV or BTOC) at Week 21, 1 cycle		
↓		
Late intensification chemotherapy at Week 48		
Etoposide and cisplatin as above, every 3 wks × 2 cycles		

group received therapeutic whole-brain irradiation, starting on Day 1 of the study, 300 cGy per daily fraction to a total of 3900 cGy in 13 fractions. Isolated bulky lesions could receive one extra dose as a boost to a total of 4200 cGy. All other patients who remained on study at Week 9 received elective whole-brain irradiation, with 300 cGy per daily fraction to a total of 3000 cGy in 10 fractions. Treatment was given using parallel opposed fields, with proper eye blocking. Dose was calculated at the central axis, midplane.

If there were involved neck nodes outside the chest field, these were treated at the same time elective brain irradiation was administered, at 300 cGy × 13 to a total of 3900 cGy, using localized ports.

Chest irradiation was given to all Group A patients remaining on study at 9 weeks. A chest x-ray performed after induction chemotherapy was used to design the portals (post-induction field), except in complete responders to induction chemotherapy, for whom the initial chest x-ray was used as an indicator of primary tumor volume. Ten daily fractions of 180 cGy were given to this initial field (total, 1800 cGy), with the intent to include all the primary tumor and abnormal lung plus a 1.5-cm margin of noninvolved lung. The mediastinum and ipsilateral hilus were always treated; the supraclavicular areas were treated in patients with known supraclavicular or mediastinal disease; and the contralateral hilus was treated if there was evidence of disease at that level. All these areas were included in a single radiotherapy port, using anterior-posterior parallel opposed fields. After 3 weeks of rest, 250 cGy per day were given for 12 more treatments to a similar field, but with a reduction of the lung field, where only obvious tumor was treated with a 1.5-cm safety margin. The total dose to the areas included in the second course was 4800 cGy, with a maximum spinal cord dose of 4500 cGy. This was achieved by the use of lateral or posterior oblique boost technique during the last few treatments or, when necessary, by use of a cord block at 4300 cGy total dose.

Therapeutic liver irradiation for Group A patients with liver metastases was initiated at completion of the first segment of chest irradiation, and the completion of elective whole-brain irradiation. The daily dose to the whole liver was 170 cGy, given in 15 fractions for a total dose of 2550 cGy. Single, isolated lesions could receive an additional five fractions at 200 cGy per day, with field size reduced to encompass the evident metastasis only.

RESULTS

A total of 456 patients were registered, ten of whom were ineligible by reason of incorrect diagnosis, stage, or prior treatment. An additional 20 patients were inevaluable (nine too early and 11 with inadequate data), leaving 426 patients (96% of those eligible) as fully or partially evaluable. All 426 are included in the analyses presented of response and survival. Groups A and B will be considered separately. Table 3 presents a summary of patient characteristics in both groups. Overall, 66% of the patients entered were fully ambulatory; clinical metastasis confined to a single extrathoracic site was present in 44%; and 22% had three or more defined extrathoracic sites. Brain metastasis was present initially in 22% (33% in Group A), and liver involvement in 47%.

In Group A, 120 patients received BTOC, with 19 complete and 46 partial responses (16% and 38%, respectively). There were 119 who received CAV, with 16 complete and 58 partial responses (13% and 49%, respectively). These differences are not significant. Neither durations of response (median, 5 months) nor of survival for all patients from entry on study (median, 7 months) were statistically different. Radiation therapy consoli-

TABLE 2.—Treatment plan for Group B patients

Induction chemotherapy at Weeks 0, 3, and 6
BTOC (*see* table 1) vs CAV (*see* table 1)
↓
Early intensification at Week 9
Elective whole-brain irradiation (*see* table 1)
Etoposide + cisplatin (*see* table 1) every 3 wks × 3 cycles
↓
Reinduction at Week 21
1 course of initial therapy (BTOC or CAV)
↓
Late intensification at Week 48
Etoposide + cisplatin every 3 wks × 2 cycles

TABLE 3.—Patient characteristics at entry on study

Characteristic	% of patients BTOC	% of patients CAV
Group A (238 patients)		
Fully ambulatory (PS 0-1)	72	72
Less than fully ambulatory (PS 2-4)	28	28
1 extrathoracic site	63	60
2 extrathoracic sites	27	28
≥ 3 extrathoracic sites	10	12
Liver metastasis	43	47
Brain metastasis	33	33
Group B (188 patients)		
Fully ambulatory (PS 0-1)	57	59
Less than fully ambulatory (PS 2-4)	43	41
1 extrathoracic site	19	22
2 extrathoracic sites	44	40
≥ 3 extrathoracic sites	37	38
Liver metastasis	55	51
Brain metastasis	8	11

dation was initiated in 136 patients (59 after BTOC and 77 after CAV), or 56% of the total. Those who did not receive consolidation either failed to respond or had response and subsequent disease progression within 9 weeks. Of these 136, categorical improvement in response category (nonresponse to partial, or partial response to complete) was observed in 24% at completion of radiation therapy. However, a similar proportion (19%) experienced disease progression during or immediately after radiation therapy, usually at sites of known disease which were not being treated at the time of relapse. Survival calculated from the start of radiotherapy for BTOC and CAV patients was the same (median, 7 months), as was time to disease progression (median, 5.5 months). Likewise, there were no differences in survival or time to disease progression when subgroups were analyzed by performance status (0-1 and 2-4) or response status (complete and partial response), with respect to the initial form of chemotherapy. However, there was a difference in toxicity. Less than fully ambulatory patients who began therapy with BTOC had more toxicity graded severe or worse ($P < 0.02$, Wilcoxon test). The major reason for this difference lies in the incidence of severe or life-threatening thrombocytopenia (23% overall after BTOC versus 8% after CAV). In turn, that difference is largely accounted for by patients with liver metastases receiving hepatic irradiation after chemotherapy, among whom the incidence of severe or life-threatening thrombocytopenia was 76% after BTOC and 14% after CAV. There were eight treatment-related deaths after BTOC (six from sepsis and two from radiation pneumonitis) and six after CAV (five from sepsis and one from radiation pneumonitis) for an overall incidence of 6%. An additional 36 patients (15%) required hospitalization at some point for the management of potentially life-threatening toxicity, virtually all hematologic. Only ten patients (4%) had nausea and vomiting rated as severe.

Of 136 patients who began irradiation consolidation, it was completed in 104 (76%). A single site was irradiated in 31; 54 received irradiation to two sites; 50 received it to three sites; and a single patient had all four possible sites irradiated. As shown in table 4, the site-specific relapse rate in areas irradiated varied from 4% for elective treatment of the whole brain to 44% for the liver. The chest relapse rate of 30% includes both in-field relapses and those occurring outside the irradiated field, but within the ipsilateral hemithorax.

In Group B, 92 patients were randomized to BTOC, while 97 received CAV. Overall response rates were 48% and 61%, respectively, with complete response in 5% versus 15% to initial induction: neither difference is statistically significant. Median response duration was 5 months and median survival was 6.5 months from the onset of chemotherapy, with no significant difference between BTOC and CAV, either for all patients or in subgroups defined by PS or response category. The major side effect of both induction treatments was myelosuppression, with 23% of patients on BTOC versus 16% on CAV who sustained life-threatening or fatal toxicity. The incidence of severe or life-threatening thrombocytopenia was 17% after BTOC and 7% after CAV. There were four treatment-related deaths after BTOC and three after CAV, all but one from sepsis, for an overall incidence of 4%. None of these differences in toxicity incidence was significant.

As shown in figure 1, the survival distribution of all patients entered is quite similar regardless of whether they were categorized as in Group A or B and independent of treatment, with a range in median from 5.9 to 8

TABLE 4.—Multiple-site irradiation consolidation in Group A patients: sites treated and sites of relapse

Site	No. of patients treated	% of patients Completing treatment at site specified	% of patients With relapse at site specified
Chest	136	81	30*
Brain (therapeutic)	33	91	24
Brain (elective)	100	98	4
Liver	48	79	44
Cervical nodes	10	70	30

*Not necessarily in treated field.

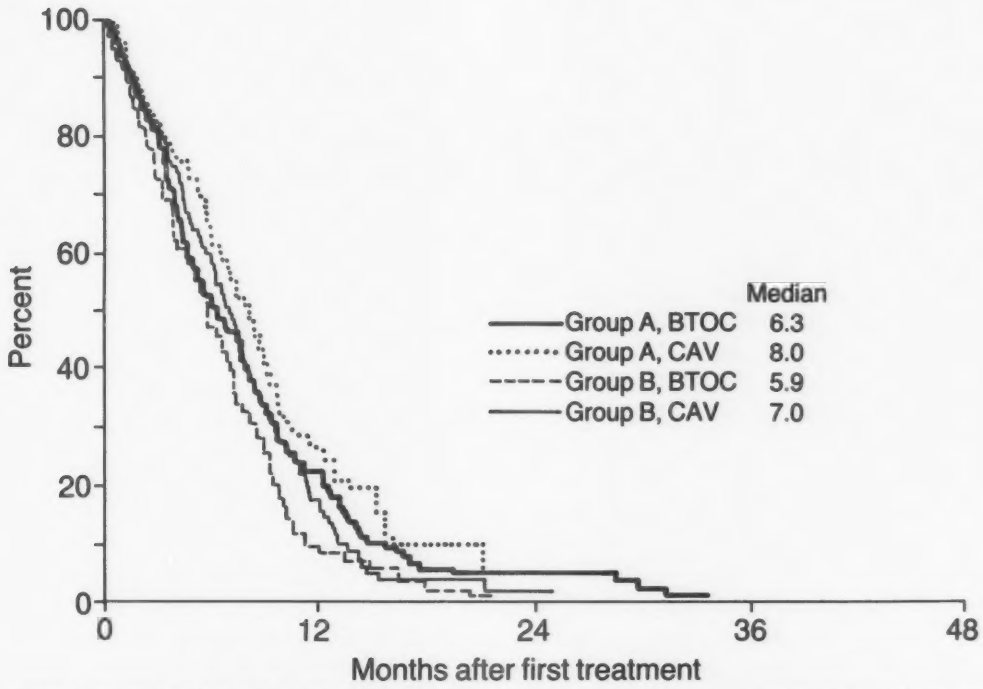

FIGURE 1.—Survival distribution of all patients entered on SWOG 8122 is similar, with a range in median survival from 5.9 to 8 months.

months. Similar comparisons were carried out for the subgroups categorized by PS (not shown), and no significant differences between treatment arms were observed in any subgroup.

A separate analysis involved patients with brain metastasis. As shown in figure 2, the survival distributions are significantly different ($P = 0.01$) if all patients entered in Group A are grouped into three categories: *brain only* (no evidence of other systemic metastases); *brain and other* (brain plus other systemic metastases); and *other only* (no evidence of brain metastases). This appears to be the result of poorer survival in the brain and other group. An analysis of sites of relapse in the group brain only revealed that only four of 22 responders (23%) had the brain as their initial site of relapse; 27% failed in the chest, and the remainder failed at new systemic sites.

Cisplatin and etoposide were generally well tolerated among patients in both Groups A and B (total, 173 treated). There were 12 patients with life-threatening myelosuppression after this combination (7%), five in Group A and seven in Group B (one fatal). Nephrotoxicity was not a reported problem. No exacerbation of peripheral neuropathy was noted with etoposide. However, improved responses were not observed after cisplatin plus etoposide, and there was no apparent effect on response duration, compared to our previous experience (4).

DISCUSSION

In spite of a solid preclinical rationale for the use of combined alkylating agents, we were unable to demonstrate improved efficacy for such a regimen (BTOC) compared to our standard CAV program at equitoxic doses. We were also unable to demonstrate any value from the use of aggressive, multiple-field consolidation to all sites of known disease with radiation therapy, although this approach proved feasible in patients selected by the criteria that we employed. It does appear that the administration of hepatic irradiation after exposure to BTOC is associated with a prohibitive incidence of high-grade thrombocytopenia, while this was not the case in patients receiving BTOC followed by irradiation other than hepatic or by other chemotherapy, even in patients with liver metastases. It rarely occurred after CAV in patients receiving hepatic irradiation. This suggests an interaction between subclinical effects of a component of BTOC (the nitrosourea?) and those of ionizing radiation directed at the liver, but the mechanism remains speculative.

Our patients with isolated brain metastases had a median survival of 8 months and 1-year survival of 38%. These results are similar to those reported from Crane et al (6) for the NCI-Navy Group, but are inferior to those reported for CNS-limited small cell patients by Van Hazel et al (7) from the Mayo Clinic. The latter group reported a median survival of 15 months in 21

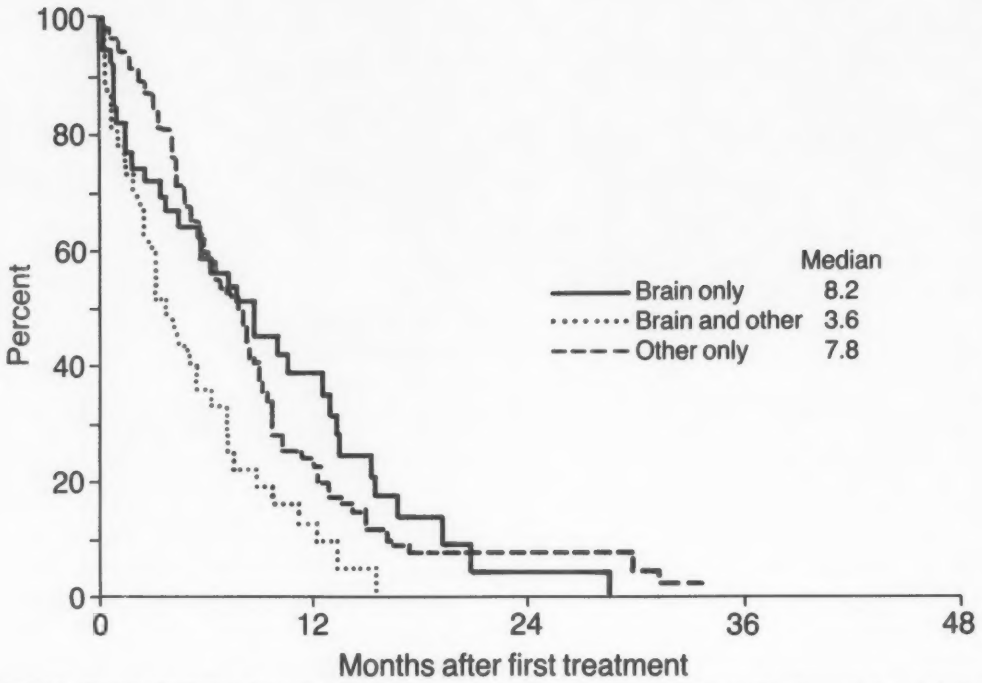

FIGURE 2.—Survival distribution of all patients entered in Group A is different ($P = 0.01$) if analyzed with reference to brain metastasis.

such patients who received a split course of 1800 cGy in five fractions, a 3-week rest, and 1800 cGy again in five fractions. None of their patients, however, experienced long-term remissions. Patients with brain metastases as their only manifestation of extensive spread do not have a worse prognosis than those with other sites of involvement, and only 23% in our experience had the brain as a clinical site of initial relapse. The latter observation suggests greater efficacy for the more intensive approach used in this protocol to therapeutic brain irradiation.

The overall median survival in this SWOG study was 7 months, which corresponds exactly to the state-of-the-art results in extensive disease as cited by Hande and Des Prez (8) in a comprehensive recent review. Table 5 summarizes the results reported from multi-institutional (cooperative group) studies of extensive small cell lung cancer over the past decade, involving nearly 3000 patients and 14 separate trials. Although there is considerable variability in reported response rates, the median survival in these studies is remarkably consistent, with a range from 4.5 to 10 months. If one includes only those trials which employed standard criteria for the definition of extensive stage, and which considered 90% or more of the eligible entries as evaluable for survival, the range further narrows (from 4.5 to approximately 8 months). Given the assortment of prognostic factors that we know can influence survival, it seems unlikely that any of these results is really different from another. Certainly, none has resulted in a substantial proportion of long-term survivors.

We feel that this trial included sufficient patients to exclude the possibility that combined alkylating agents offer an advantage (at doses tolerable in an outpatient setting) over CAV (power of 0.8 to detect a response rate difference of 20% at $P \leq 0.05$). Further, with systemic therapy of present effectiveness, a maximally aggressive policy of multiple-site, local-field irradiation appears fruitless. However, it is feasible and might prove more effective if the proportion of patients achieving complete response to systemic treatment could be increased. Finally, we could demonstrate no value to the administration of cisplatin and etoposide as a putatively non-cross-resistant combination to patients in remission, after induction with other drug regimens, in terms of either improved response quality or prolonged remission duration.

TABLE 5.—Cooperative group studies in extensive small cell lung cancer, 1976–1985: response rate and survival

Ref No.	Group*	No. of patients	Response rate (%)		Median survival (mos)	Year published
			Complete	Overall		
9	ECOG	184	3–12	22–43	4–5	1976
10	Denmark	109	—	75–78	6–7.6	1978
11	SWOG	250	14	57	6	1978
12	SEG	207	9	57	7	1979
13	SWOG	254	5	46–50	6.5	1980
14	CALGB	119	10	—	4.7	1981
15	SAKK	73	23	67	5–7.5	1981
16	ECOG	246	10	54–64	7–8	1982
17	ECOG	254	10	44–57	6	1982
18	NCOG	106	20–42	53–63	7–10†	1984
19	POG	74	8–30	38–85	6.7–9.0	1984
20	SEG	293	24	72–74	9.5‡	1984
21	SWOG	429	16	61	7.5	1984
22	CALGB	~300	—	—	7.6–9.2	1985

*ECOG = Eastern Cooperative Oncology Group; SEG = Southeastern Cancer Study Group; CALGB = Cancer and Leukemia Group B; SAKK = Swiss Group for Clinical Cancer Research; NCOG = Northern California Oncology Group; and POG = Piedmont Oncology Association.

†One-third had limited disease by criteria of other groups.

‡24% of patients eligible were excluded as inevaluable.

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Clinical Pharmacology of Homoharringtonine[1]

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Clinical pharmacokinetics of homoharringtonine (HHT) were studied in eight patients who received uniformly labeled HHT at 3–4 mg/m^2 (150 μCi) by continuous 6-hour infusion. The drug and metabolites were quantified by radiochemical and high-performance liquid chromatographic techniques. Computerized nonlinear least-square regression and curve stripping were used to characterize HHT and total [^{3}H]HHT equivalent pharmacokinetics. Unchanged HHT in the plasma declined biphasically, with an α-half-life of 0.5 ± 0.1 hours and a β-half-life of 9.3 ± 1.4 hours. The total clearance of HHT was 177.4 ± 27.7 ml·hour^{-1}·kg^{-1}, and the apparent volume of distribution, estimated from the area under the drug concentration versus time curve, was 2.4 ± 0.4 L·kg^{-1}. Correspondingly, the total [^{3}H]HHT equivalent disappeared from the plasma in a triphasic manner. Compared with the pharmacokinetic parameters of unchanged HHT, the terminal half-life of total ^{3}H was 67.5 ± 7.5 hours, 7.4 times longer; the total clearance was 30.9 ± 3.1 ml·hour^{-1}·kg^{-1}, 5.5 times slower; but the volume of distribution by area was 2.7 ± 0.1 L·kg^{-1}, nearly the same. The 72-hour cumulative urinary excretion of total tritium was 28.2% of the administered dose and only 38.3% of this resided in unchanged HHT. Thus, urinary excretion was not a major route of elimination of HHT. Moreover, HHT underwent extensive metabolism; one major and two minor unidentified products were detected in both plasma and urine. [Cancer Treat Rep 70: 1403–1407, 1986]

In the search for new antitumor agents of plant origin, a number of cephalotaxine derivatives have been isolated from several species of cephalotaxus (1,2). Among them homoharringtonine (HHT) (fig 1), harringtonine, isoharringtonine, and deoxyharringtonine have shown antitumor activity. HHT, the most thoroughly investigated derivative, is active against experimental tumor systems including P388 leukemia, L1210 leukemia, Lewis lung carcinoma, colon carcinoma 38, and epidermoid carcinoma of the nasopharynx (KB cell culture) (3,4). In addition, in Chinese literature, a mixture of harringtonine and HHT was active against L615 mouse reticulum cell leukemia, B22 mouse brain tumor, S180 mouse sarcoma, and rat 256 Walker carcinosarcoma (5). In 1976, the Chinese reported that the drug produced clinical remission in patients with acute leukemias (5). On the strength of these findings, HHT was chosen for phase I clinical trial at the University of Texas M. D. Anderson Hospital and Tumor Institute. Toxic effects included myelosuppression, hypotension, and tachycardia; the maximum tolerated dose was 4 mg/m^2 × 5 days (6). Phase II trials in multiple solid tumors have also been recently performed. In conjunction with our phase II trial, we have investigated the clinical pharmacology of HHT.

MATERIALS AND METHODS

Uniformly tritiated HHT was prepared by the Amersham Corporation, Arlington Heights, IL, with a chemical purity of 85% by high-performance liquid chromatography (HPLC) and a specific activity of 191 mCi/mmol. This material was free of exchangeable tritium. Unlabeled HHT was supplied by the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD. Glass-distilled chromatographic solvents were purchased from Burdick and Jackson Laboratories, MI. Other chemicals and reagents were from regular commercial sources.

Patients

Patients with histologically proven cancer, a minimal age of 15 years, and normal liver and kidney functions were entered in this study. Informed consent was ob-

[1] Received Aug 15, 1985; revised July 29, 1986; accepted Aug 20, 1986.

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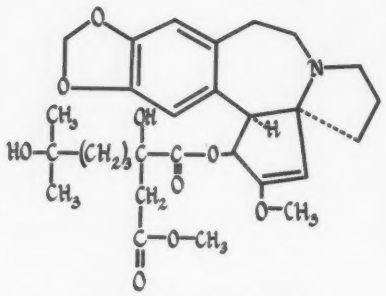

FIGURE 1.—Structure of HHT.

tained from all patients according to institutional guidelines. HHT at the desired dose admixed with 150 μCi of the radiolabeled drug (an amount approved by our institutional radiation safety committee) was dissolved in 1 L of normal saline and administered by continuous 6-hour infusion by means of a McGraw volumetric infusion pump. On subsequent days the same dose of the unlabeled drug was infused. Blood was drawn at intervals from an indwelling heparin lock for 72–96 hours, and urine was collected as voided for 72 hours.

Radiochemical Technique

A plasma or urine specimen (0.2 ml each) was mixed with 11 ml of PCS (a phase-combining counting solution available from the Amersham Corporation), and the radioactivity therein was determined with a Packard Tri-Carb Model 2650 liquid scintillation spectrometer equipped with an automatic self-calibration quenching device.

Chromatography

Plasma or urine (2 ml each) was extracted twice with 6 ml of methylene chloride each time and centrifuged at 12,000 × *g* with an efficiency > 90%. The combined organic phase was removed and evaporated to dryness under a stream of nitrogen. The residue was reconstituted with 500 μl of the mobile phase. The HPLC was equipped with a μBondapak C18 reverse-phase column, a Waters variable wavelength UV detector, and a data module. The mobile phase consisted of 0.1 M ammonium formate (pH 6.0) in 40% MeOH, and the flow rate was 2.0 ml/minute. The UV monitor was set at 284 nm.

Sufficient unlabeled HHT was added to all samples as a marker. The eluent was collected at 1-minute intervals. The presence of HHT was revealed in a peak as detected by UV absorbance at 284 nm; the entire volume of this peak was collected. The added radioactive HHT in the plasma had 85% purity by this method. The rest of the radioactivity accounted for the impurity eluted at 1–2 minutes. The amount of radioactivity added is very small (430 μg) when compared with the nonradioactive drug (3–4 mg/m^2). Therefore, the amount of impurity was negligible; however, to correct the variation between patients, a standard curve was performed for each patient.

HHT Standard Curve

A specimen of 0.1 ml of the drug was taken from the infusion bag; serial dilution was made with the patient's own plasma and extracted as above. The extracts were analyzed for HHT. The standard curve was linear from 5 to 100 ng/ml and the lowest limit of detection was 5 ng/ml.

HHT Metabolite

Trichloroacetic acid (20%) was added to the aqueous layer from the methylene chloride extraction. The mixture was centrifuged at 12,000 × *g* and the supernatant was adjusted to pH 6.0 with KOH and analyzed by HPLC as described above. HHT eluted at 12 ± 1 minutes and its major metabolite at 6 ± 1 minutes. The two minor metabolites present in the organic layer eluted at 30 and 38 minutes.

Pharmacokinetic Analysis

The plasma HHT data were subjected to nonlinear least-square regression analysis with the aid of a CYBER, 174 computer system, using the ESTRIP and NONLIN programs. All data points were appropriately weighted with reciprocal drug concentration. The comparison was made by correlation coefficient; either a two- or three-compartment open model produced the best results. Pharmacokinetic parameters were computed by standard techniques (7) and corrected for infusion time by the method of Loo and Reigelman (8).

The integral of the entire postinfusion concentration time (AUC) was calculated by:

$$\text{Area} = \frac{A'}{\alpha} + \frac{B'}{\beta},$$

where A′ and B′ were zero time intercepts and corrected for infusion time as follows:

$$A' = \frac{A\alpha T}{1-e^{-\alpha T}}$$

$$B' = \frac{B\beta T}{1-e^{-\beta T}},$$

where T was the infusion time.

The volume of distribution at the central compartment Vc was calculated by:

$$Vc = \frac{Do}{A' + B'},$$

where Do is the total dose given.

The volume of distribution by area (Vda) was calculated by:

$$Vda = \frac{\text{Clearance}}{\beta}$$

TABLE 1.—Pharmacokinetic parameters of HHT

Patient No.	Dose (mg/m^2)	Half-lives (hrs) α	Half-lives (hrs) β	Clearance rate ($ml \cdot hr^{-1} \cdot kg^{-1}$)	Vda ($L \cdot kg^{-1}$)	Vdss ($L \cdot kg^{-1}$)	Vc ($L \cdot kg^{-1}$)	K_{12} (hr^{-1})	K_{21} (hr^{-1})	K_{10} (hr^{-1})
1	4	0.2	7.4	86	1.0	0.7	0.1	1.87	0.27	1.01
2	3	0.4	11.3	170	2.8	2.0	0.3	1.17	0.19	0.59
3	4	0.1	2.5	149	0.6	0.3	0.1	3.18	0.62	2.72
4	4	1.1	13.3	169	3.3	2.8	1.1	0.32	0.22	0.15
5	4	0.2	8.8	129	1.6	1.4	0.3	2.16	0.48	0.50
6	3	.3	8.4	289	3.5	2.7	0.4	1.84	0.31	0.78
7	4	0.7	7.9	304	3.5	2.4	1.8	0.38	0.45	0.17
8	3	0.8	14.7	123	2.6	1.9	0.4	0.50	0.14	0.29
Mean ± SE		0.5 ± 0.1	9.3 ± 1.4	177.4 ± 27.7	2.4 ± 0.4	1.8 ± 0.3	0.6 ± 0.2	1.43 ± 0.36	0.34 ± 0.06	0.78 ± 0.30

The volume of distribution at steady-state (Vdss) was calculated by:

$$Vdss = Do \times \frac{A'\beta^2 + B'\alpha^2}{(A'\beta + B'\alpha)^2}$$

Total-body clearance was calculated by:

$$Cl_T = \frac{Do}{\frac{A'}{\alpha} + \frac{B'}{\beta}}$$

The apparent first-order intercompartmental distribution rate constants K_{12} and K_{21} and first-order elimination constant were calculated by:

$$K_{12} = \frac{A'B' \cdot (\beta - \alpha)^2}{A' + B' (A' \cdot \beta + B' \cdot \alpha)}$$

$$K_{21} = \frac{A'\beta + B'\alpha}{A' + B'}$$

$$K_{13} = \alpha + \beta - K_{12} - K_{21}$$

RESULTS

The pharmacokinetic parameters of unchanged HHT are shown in table 1. HHT disappeared from plasma biphasically with a mean half-life of 9.3 ± 1.4 hours during the terminal phase. In contrast, the total radioactivity disappeared triphasically with a relatively long half-life of 65.3 ± 6.4 hours (table 2), 7.4 times longer than that of unchanged HHT (fig 2). At 24 hours, HHT was no longer detectable in the plasma of all eight patients studied. One major metabolite was found in the plasma of all patients; its concentration peaked at 2–6 hours in all patients and in four patients it peaked again at 24 or 48 hours. The average half-life of this metabolite in four patients was 84.3 ± 7.5 hours. Additionally, two other minor metabolites that eluted at 30 and 38 minutes were detected in the urine in all patients and in the plasma of some. The average 72-hour cumulative urinary excretion of HHT in eight patients was 10.8% ± 0.8% of the dose (table 3). In the same time period, about the same percentage of the dose was excreted as a major metabolite. The total radioactivity excreted in 72 hours was > 20%. Figure 3 shows the cumulative urinary excretion in one patient up to 96 hours. In one patient who developed moderate hypotension during HHT administration, the plasma drug concentration at steady state was relatively low as compared with those in two other patients at the same dose, ie, 25 versus 50 ng/ml. However, the other pharmacokinetic parameters were not remarkably different.

DISCUSSION

HHT has some activity against human acute myelocytic leukemia (9). Information is scant on its pharmacokinetics; the only publication on this subject appeared in Chinese medical literature not readily available

TABLE 2.—Pharmacokinetic parameters of total [^{3}H]HHT

Patient No.	Half-lives (hrs) α	Half-lives (hrs) β	Half-lives (hrs) γ	Clearance rate ($ml \cdot hr^{-1} \cdot kg^{-1}$)	Vda ($L \cdot kg^{-1}$)	Vc ($L \cdot kg^{-1}$)
1	0.1	2.3	53.1	31.9	2.5	0.1
2	0.3	9.7	67.4	32.2	3.1	0.3
3	0.2	2.3	60.5	26.9	2.3	0.2
4	0.02	2.6	39.5	48.2	2.7	0.1
5	0.1	6.1	79.8	24.3	2.8	0.9
6	0.7	1.7	48.7	37.5	2.6	0.4
7	1.1	13.4	90.0	24.2	3.1	0.7
8	0.4	4.2	83.5	21.6	2.6	0.8
Mean ± SE	0.4 ± 0.1	5.3 ± 1.5	65.3 ± 6.4	30.9 ± 3.1	2.7 ± 0.1	0.4 ± 0.1

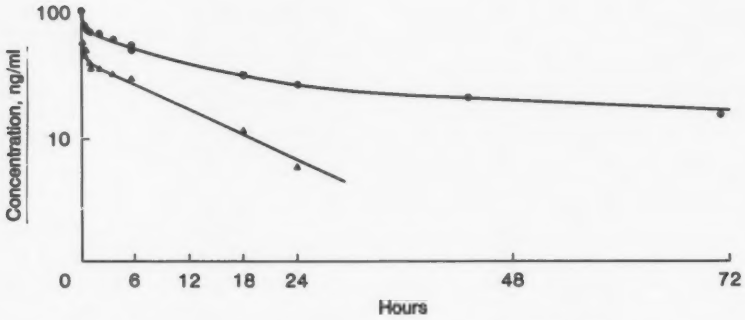

FIGURE 2.—Plasma disappearance of HHT and total ^3H. ●——● = total ^3H and ▲——▲ = HHT.

TABLE 3.—Cumulative urinary excretion

Patient No.	% dose in 72 hrs		
	Total ^3H	HHT	Major metabolite
1	32.6	9.3	6.6
2	28.8	13.2	15.7
3	42.1	8.7	6.3
4	24.2	9.3	3.7
5	23.4	9.6	11.0
6	20.3	13.0	7.3
7	31.9	14.0	12.6
8	22.1	9.9	9.0
Mean ± SE	28.2 ± 2.5	10.8 ± 0.8	9.0 ± 1.4

in the United States. Because of methodological ambiguity, their results are difficult to interpret.

From our studies, it is readily apparent that in man HHT is rapidly and extensively metabolized; the overall pharmacokinetic characteristics of the metabolites are distinctly different from those of HHT itself. Computed from the area under the plasma drug concentration-versus-time curve, the mean apparent volume of distribution of HHT is about the same as that of the total radioactivity residing in HHT and metabolites, ie, 2.4 versus 2.7 $L \cdot kg^{-1}$. However, the total clearance of HHT, 177.4 $ml \cdot hour^{-1} \cdot kg^{-1}$, is 5.5 times as large as that of the total radioactivity, 30.8 $ml \cdot hour^{-1} \cdot kg^{-1}$. As a result, the plasma half-life of HHT is sevenfold shorter than that of the total radioactivity, 9.3 versus 65.3 hours.

Furthermore, in 72 hours 28.2% of the administered radioactivity was excreted in the urine, including 10.8% as the unchanged drug and another 9.0% as the major metabolite. Evidently, urinary excretion plays only a minor part in the elimination of HHT in man; the major routes must, therefore, be by metabolism or tissue sequestration or both. The role of hepatobiliary excretion in HHT elimination is likewise uncertain; however, it is probably minor because we observed that in the dog merely 2% of the dose was excreted in 6 hours (10). Unfortunately, in our studies feces were not reliably collected from patients for HHT analysis to verify this point.

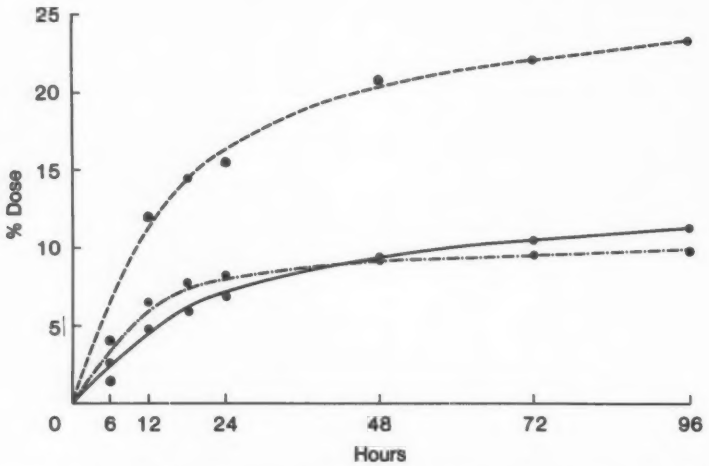

FIGURE 3.—– = cumulative urinary excretion of total ^3H; ·—— = cumulative urinary excretion of HHT; and —— = cumulative urinary excretion of M_1 metabolite.

The rapid extensive metabolism of HHT in man is reminiscent of our in vitro investigation (11). Incubation of HHT with rat hepatic microsomal preparations resulted in 30% degradation of the drug in 60 minutes (11). The structures of the metabolites remain to be elucidated; the overall pharmacokinetic properties of these metabolites are very different from those of HHT itself. Not only were the half-lives of the metabolites much longer than those of HHT, but also the plasma concentrations of the major metabolite peaked first at 2–6 hours, then again at 24 or 48 hours. Such an undulation could be attributed to tissue binding or enterohepatic recirculation of this metabolite. Also, the metabolites may differ significantly from HHT in their anticancer and cytotoxic properties.

The mechanism of hypotension after HHT administration is obscure. In phase I trials of HHT, hypotension and tachycardia occurred 6–10 hours following HHT therapy and were accompanied by a 30%–80% increase in cardiac output (6), suggesting that HHT may have caused a reduction in peripheral vascular resistance. In one patient studied by us during the hypotensive episode, no changes in pharmacokinetic parameters were noted except for an apparently lower steady-state HHT concentration in the plasma. Whether or not this was the result of an enhanced receptor binding needs to be further investigated.

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Safe, Rapid Administration of Cisplatin in the Outpatient Clinic[1,2]

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The records of 147 cancer patients who received at least three courses of cisplatin-containing chemotherapy in the Arizona Cancer Center clinic between 1982 and 1985 were reviewed to determine the safety and tolerance of cisplatin administered in the outpatient setting. Cisplatin was administered at doses of 50–120 mg/m^2 every 3–4 weeks. The drug was added to 400 ml of 10% mannitol, was brought up to 1-L volume with normal saline containing 3 g of magnesium sulfate, and was administered iv over 1 hour. An additional liter of normal saline was administered over approximately 1 hour in patients who received cisplatin doses of 70–120 mg/m^2. Courses were interrupted if the serum creatinine was > 1.5 mg/dl just prior to the next scheduled dose. The median total doses of cisplatin per patient were 487, 595, and 683 mg/m^2 and complete plus partial response rates were 64%, 71%, and 78% for those patients who received 50–60, 70–90, and 100–120 mg/m^2/course, respectively. Cisplatin-containing therapy was tolerated without evidence of renal failure and with only moderate to severe emesis in 25% of the patients. Calculated creatinine clearances dropped only 4.9%, 13.9%, and 14.9% between Courses 1 and 6 in patients receiving cisplatin doses of 50–60, 70–90, and 100–120 mg/m^2, respectively. We conclude that cisplatin doses of 50–120 mg/m^2 can be administered safely and with acceptable tolerance in the outpatient setting. [Cancer Treat Rep 70:1409–1414, 1986]

Cisplatin has become one of the most commonly used drugs in the treatment of advanced cancer. It has proven to be a useful drug in patients with advanced ovarian, lung, bladder, cervix, head and neck, and testicular cancers (1–12). Because its administration requires adequate pre- and/or post-hydration with normal tonic saline solutions (13–15) to protect against cisplatin-induced nephrotoxicity (16–19), patients are frequently admitted to the hospital to facilitate treatment. Such hospitalizations are expensive and time-consuming, especially for the large percentage of patients who are likely to die of progressive cancer.

We have reported previously (20) that patients treated with intermediate doses of cisplatin (ie, 50–80 mg/m^2) can be hydrated safely in the outpatient department with a minimum amount of normal saline. Since 1976, patients treated at the Arizona Cancer Center with cisplatin have received the anticancer drug diluted in 1 L of normal saline over a period of 1 hour (20). Our previous report concerning this drug administration schedule suggested that nephrotoxicity from cisplatin was only mild in degree and relatively infrequent (20). More recently, Vogl et al (21) have advocated a 2-hour regimen of diuresis and hydration as being safe and tolerable for the patient receiving cisplatin in the clinic. In the present study, we have updated our experience concerning the toxicity associated with rapid administration of cisplatin in the outpatient setting.

METHODS

Patients

Between 1982 and 1985, > 200 patients were treated at the Arizona Cancer Center outpatient facility with cisplatin as a single agent or as a part of combination-chemotherapy programs for their advanced cancers. All patients treated in the Arizona Cancer Center outpatient facility who had serum creatinine determinations prior to and 4 weeks following each of at least three courses of cisplatin therapy were evaluated in this study. To avoid selection bias, patients were excluded from evaluation only if they had received cisplatin treatment during hospitalization (eg, received treatment in the hospital because of transportation difficulties between

[1] Received Nov 25, 1985; revised Aug 11, 1986; accepted Aug 20, 1986.
[2] Supported in part by Public Health Service grants CA-17094 and CA-23074 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services, and by a grant from Bristol Laboratories, Syracuse, NY.

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their homes and the Cancer Center clinic) or received fewer than three courses of cisplatin-containing therapy. The latter exclusion was used because no patient who received fewer than three courses of cisplatin between 1982 and 1985 experienced drug-related nephrotoxicity. These patients had treatment terminated because of tumor progression in the absence of significant toxicity.

Prior to each course of cisplatin-containing therapy, all patients had a physical examination, including Karnofsky performance status (PS) evaluation, and blood was obtained for wbc count, hemoglobin, hematocrit, platelet count, serum creatinine, and SMA-20 determinations.

Cisplatin Administration

Cisplatin was administered at doses ranging from 50 to 120 mg/m^2 iv once every 3–4 weeks. The drug was prepared in the outpatient clinic and reconstituted in sterile water to a dose of 1 mg/ml, added to 400 ml of 10% mannitol, and brought up to a 1-L volume with normal saline containing 3 g of magnesium sulfate. The 1-L volume containing cisplatin was administered over a 1-hour period. An additional liter of normal saline was administered over approximately 1 hour in patients who received cisplatin doses of 70–120 mg/m^2. Courses were interrupted if the serum creatinine was > 1.5 mg/dl just prior to the next scheduled cisplatin course. Treatment was reinitiated as soon as the serum creatinine fell to ≤ 1.5 mg/dl.

Antiemetic Regimens

Between 1982 and 1985, two antiemetic trials were initiated at the Arizona Cancer Center (22–24). The first trial involved a randomized, double-blinded study of high-dose metaclopramide versus high-dose dexamethasone designed to facilitate outpatient administration (22). Thirty-four patients were entered in this study. The second trial involved a combination of five antiemetics, again designed specifically for outpatient use, and consisting of metaclopramide, thiethylperazine, diphenhydramine, dexamethasone, and diazepam (23,24). Seventy-one patients receiving cisplatin-containing chemotherapy regimens received 170 courses of this five-drug combination.

Calculation of Creatinine Clearance

Creatinine clearance was determined for all patients each time a serum creatinine was obtained using the equation of Cockcroft and Gault (25) as shown below for males:

$$C\,cr = \frac{(140 - age)\,(weight\ in\ kg)}{72 \times S_{cr}\ (mg/100\ ml)}$$

Creatinine clearance was calculated for females by multiplying the right side of the above equation by a factor of 0.85.

Response Criteria

Standard criteria were used to evaluate response. Complete clinical response was defined as the disappearance of all measurable disease for > 1 month. Partial response was defined as a $> 50\%$ reduction in the sum of the products of the largest perpendicular diameters of all measurable tumors for > 1 month. Disappearance of cytologically positive malignant effusions for > 1 month was also included in this response category. No response was defined as a $< 50\%$ reduction in measurable disease, partial clearance of malignant effusions, or no evidence of change in disease status.

RESULTS

Patient Data

One hundred forty-seven patients were fully evaluable with respect to cisplatin-induced toxicity following outpatient drug administration. Patient characteristics and cisplatin dosing and response data are shown in tables 1 and 2, respectively. Note that the 147 patients have been divided into three groups according to cisplatin dosage. Group 1 included 112 patients who received at least three courses of cisplatin at 50–60 mg/m^2. Group 2 included 17 patients who received at least three courses of cisplatin at 70–90 mg/m^2. Group 3 included 18 patients who received at least three courses of cisplatin at 100–120 mg/m^2. The median ages for Group 1–3 patients were 57, 57, and 43 years, respectively. Thirty-seven percent of the patients were males and 63% were females. Forty-one percent of the patients had gynecologic cancers, 31% had lung cancers, and 25% had cancers of other types (eg, genitourinary, gastrointestinal, and head and neck cancers). The median total dose of cisplatin per patient was 487 mg/m^2 for those who received 50–60 mg/m^2, 595 mg/m^2 for those who received 70–90 mg/m^2, and 683 mg/m^2 for those who received 100–120 mg/m^2. The complete plus partial response rates for pa-

TABLE 1.—Patient characteristics grouped according to cisplatin dose

Group No.	No. of patients	Cisplatin dose/course (mg/m^2)	Patient age in yrs (mean ± SE)	Sex (ratio M:F)	Tumor type (%)		
					Gynecologic	Lung	Other
1	112	50–60	57 ± 1	1:2.0	49	35	16
2	17	70–90	57 ± 4	1:1.1	12	29	59
3	18	100–120	43 ± 4	1:1.0	17	39	44

TABLE 2.—Cisplatin dosing and response data for 178 evaluable patients

Group No.	No. of patients	Cisplatin dose/course (mg/m^2)	% of patients receiving — 3 courses	4-6 courses	>6 courses	Mean total dose of cisplatin (mg/m^2)	Response to cisplatin-containing therapy (%) Complete	Partial
1	112	50-60	20	51	30	487	27	37
2	17	70-90	41	41	18	595	24	47
3	18	100-120	39	56	6	683	22	56

tients who received 50-60, 70-90, and 100-120 mg/m^2 were 64%, 71%, and 78%, respectively.

Creatinine Clearance Data

Tables 3 and 4 show the mean creatinine clearances prior to each cisplatin treatment course for patients who received at least three or six courses of therapy, respectively. Figure 1 shows the mean (± SE) creatinine clearances for each of the three groups of patients over three or six courses of cisplatin-containing chemotherapy. As shown in table 3, creatinine clearances dropped 4.6%, 12.2%, and 1.5% between Courses 1 and 3 in patients receiving cisplatin doses of 50-60, 70-90, and 100-120 mg/m^2, respectively. Between Courses 1 and 6 of cisplatin-containing chemotherapy, the mean creatinine clearance dropped 4.9%, 13.9%, and 14.9% for patients who received cisplatin doses of 50-60, 70-90, and 100-120 mg/m^2, respectively (table 4). Statistical tests to evaluate whether these changes in mean creatinine clearance over time for all dosing groups were significant showed a P value of < 0.05 in patients who received three courses of treatment and a P value of < 0.06 in patients who received six courses of treatment. During the study period (ie, 1982-1985), no patient experienced cisplatin-induced renal failure requiring medical management. Only five patients (3.4%) required interruption of cisplatin therapy because of interim rises in serum creatinine > 1.5 mg/dl.

Performance Status Data

Serial performance status data were available for 89 of the 147 patients. Pre- and post-cisplatin performance status evaluations for 71 patients treated with a cisplatin dose of 50-60 mg/m^2 and nine patients each treated at doses at 70-90 and 100-120 mg/m^2 for all courses of cisplatin therapy are shown in table 5. For patients who received doses of 50-60 mg/m^2 there was a decrease of 3% in performance status. There was an increase of 7.6% in performance status for the nine patients treated at 70-90 mg/m^2 and a decrease of 19.3% in performance status for the nine patients treated at 100-120 mg/m^2.

TABLE 3.—Mean creatinine clearance data for patients treated with at least 3 consecutive courses of cisplatin-containing chemotherapy

No. of patients	Cisplatin dose (mg/m^2)	Mean creatinine clearances prior to each cisplatin treatment course 1	2	3
112	50-60	76.1	74.5	72.6
17	70-90	76.0	70.7	66.7
18	100-120	96.5	93.8	95.1

Antiemesis Data

Data concerning the presence or absence of emesis during any course of treatment in the 143 patients who were entered prospectively in antiemetic trials are shown in table 6 (22-24). Sixty-one percent of the 115 patients treated with cisplatin doses of 50-60 mg/m^2 experienced at least one episode of emesis. Fifty-four percent of the 13 patients treated with 70-90 mg/m^2 and 53% of the 15 patients treated with 100-120 mg/m^2 experienced at least one episode of emesis. Thus, 39%-47% of all patients entered in the antiemetic trials and treated with cisplatin-containing therapy were free of emesis during all treatment courses.

DISCUSSION

Since 1976, cisplatin administration to Arizona Cancer Center patients has been designed to facilitate outpatient care (20). Because of the small size of the University Medical Center and our desire to limit hospital admissions for cancer patients, > 90% of cisplatin treatments have been administered on an outpatient basis. The cisplatin dose is administered in 1 L of normal saline over a 1-hour period and only those patients who receive cisplatin doses ≥ 100 mg/m^2 are given an additional liter of saline over a 1-hour period to assure adequate hydration. During this 9-year period, no patient has developed cisplatin-induced renal failure requiring medical intervention. Because of the exceptional safety record of cisplatin administration in our outpatient program (20) and our desire to demonstrate that this drug can be routinely administered on an outpatient basis, we have carried out a retrospective evaluation of the safety and tolerance of outpatient cisplatin treatment between 1982 and 1985.

Of the 147 patients evaluated in this study, 112 received cisplatin doses of 50-60 mg/m^2, for a minimum of three courses. There was only a 4.6% drop in the mean calculated creatinine clearance for this patient group.

TABLE 4.—Mean creatinine clearance data for patients treated with at least 6 consecutive courses of cisplatin-containing chemotherapy

No. of patients	Cisplatin dose (mg/m^2)	Mean creatinine clearances prior to each cisplatin treatment course					
		1	2	3	4	5	6
24	50–60	67.3	68.7	66.7	68.4	67.3	64.0
4	70–90	82.7	75.1	69.8	76.3	75.4	71.8
3	100–120	108.2	98.4	100.0	113.3	105.0	92.1

For the 18 patients who received doses of 100–120 mg/m^2 for a minimum of three courses, there was only a 1.5% decrease in mean calculated creatinine clearance. These data suggest that outpatient cisplatin therapy can be administered safely for at least three courses of treatment. Similar data for changes in creatinine clearance were observed for patients who received 50–60 mg/m^2 of cisplatin for a minimum of six courses. Creatinine clearance decreased by only 4.9% between the first and sixth course of therapy. Too few patients were treated at the 70–90- and 100–120-mg/m^2 cisplatin doses for a minimum of six courses to draw final conclusions concerning the safety of cisplatin over a 6-month period. Nevertheless, the limited patient data for 70–90 and 100–120 mg/m^2 suggest that these high doses of cisplatin were well-tolerated by those who received all treatment in the outpatient department.

The significantly higher creatinine clearances observed in patients treated with cisplatin doses of 100–120 mg/m^2 can be explained by the younger age of this patient group (ie, mean age, 41 years; table 1). These patients averaged 16–17 years younger than patients who received the lower doses of cisplatin. The major reason for this discrepancy relates to the fact that most of these younger patients had lung cancer and were entered in clinical trials which called for the 100–120-mg/m^2 doses of cisplatin.

Changes in Karnofsky performance status represent

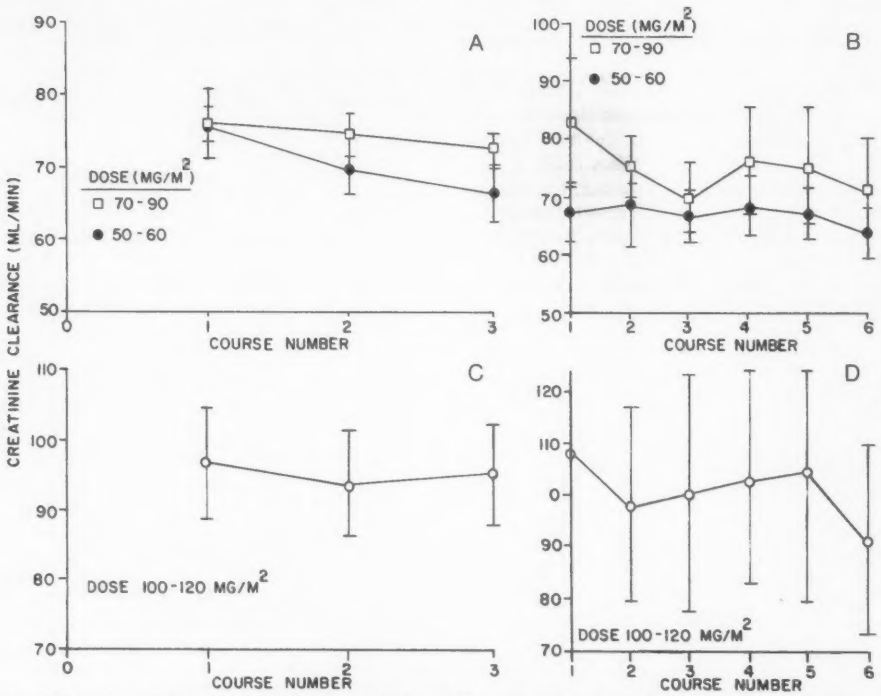

FIGURE 1.—Calculated creatinine clearances prior to each of 3 (Panel A) or 6 (Panel B) courses of cisplatin-containing therapy in groups of patients receiving doses of 50–60 or 70–90 mg/m^2 every 3–4 wks in the outpatient clinic. Calculated creatinine clearances prior to each of 3 (Panel C) or 6 (Panel D) courses of cisplatin-containing therapy in patients receiving doses of 100–120 mg/m^2 every 3–4 wks in the outpatient clinic.

TABLE 5.—Pre- and post-cisplatin Karnofsky performance data for 89 patients

No. of patients	Cisplatin dose (mg/m^2)	Karnofsky performance status (%)	
		Pre-cisplatin	Post-cisplatin
71	50–60	76.5	74.2
9	70–90	73.3	78.9
9	100–120	86.7	70.0

TABLE 6.—Emesis data for 143 cisplatin-treated patients entered in antiemetic trials

No. of patients	Cisplatin dose (mg/m^2)	At least 1 episode of emesis (%)	No episodes of emesis (%)
115	50–60	61	39
13	70–90	54	46
15	100–120	53	47

an effective way to evaluate the tolerance of cisplatin therapy administered in the outpatient department. We observed that there was no clinically significant change in the mean performance status data for patients who received up to six courses of treatment with cisplatin at doses of 50–60 mg/m^2. On the other hand, the mean performance status for the nine patients who received 100–120 mg/m^2 of cisplatin decreased by 19%. Other factors besides cisplatin treatment may have influenced the significant clinical deterioration observed in this group. Specifically, most of these patients had lung cancer and > 60% did not respond to chemotherapy. Thus, it would be unjustified to suggest that the cisplatin treatment was mainly responsible for this clinical deterioration. Furthermore, the nine patients treated with intermediate doses of cisplatin in the outpatient department (ie, 70–90 mg/m^2) experienced an 8% improvement in Karnofsky performance status while receiving cisplatin chemotherapy. Most of these patients had ovarian cancer and experienced a > 70% objective response rate to chemotherapy.

Cisplatin-based chemotherapy was relatively well-tolerated in the outpatient setting with respect to the incidence of severe nausea and vomiting (table 5). From 39% to 47% of the patients experienced no episodes of emesis while being treated with up to six courses of cisplatin-containing chemotherapy. Our data were collected prospectively as a result of well-controlled antiemetic trials that were on-going in our outpatient clinic between 1982 and 1985 (22–24). The majority of patients treated with cisplatin doses > 60 mg/m^2 were treated with a new five-drug antiemetic regimen designed specifically for outpatient use (24). Almost 50% of these patients had no episodes of vomiting throughout their cisplatin treatment courses. Another 25% of the patients had fewer than three episodes of emesis. Thus, approximately 75% of the patients treated with intermediate and high doses of cisplatin-containing chemotherapy were relatively well-protected from emesis. Although further improvements in antiemetic regimens are needed and anticipated, our data suggest that even high doses of cisplatin can be administered in the outpatient setting with good patient tolerance.

Now that the diagnosis-related group methods for reimbursement of hospital expenses have become a factor in medical management, more effective ways of administering anticancer drug treatments in the outpatient department are needed. We believe that our retrospective data prove that cisplatin, even in high doses, can be administered safely and with good tolerance to patients in the outpatient setting. Such approaches to patient management are likely to both decrease the cost of medical care and improve the quality of life of cancer patients; however, before our study results can be generalized for all patient populations, it will be necessary to obtain additional safety and tolerance data for cisplatin administration at high doses (eg, 100–120 mg/m^2) in older patients (eg, ages > 60 years).

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Therapeutic and Pharmacokinetic Relationships of Flavone Acetic Acid: An Agent With Activity Against Solid Tumors[1,2]

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Flavone acetic acid is a novel structure which exhibits an interesting spectrum of antitumor activity in preclinical studies. It has little antitumor activity in the leukemias and pronounced antitumor activity in solid tumors. Preclinical therapeutic, toxicologic, and pharmacokinetic studies are summarized and considered together to introduce the concept of a therapeutic window of effective plasma concentrations and effective exposure times in attempts to maximize therapeutic effects and minimize toxic effects. Plasma concentrations, predicted to fall from 600 to 100 μg/ml over 10 hours resulting from 267 mg/kg ip bolus injections in mice are curative to sc implanted colon 38. Doses of 356 mg/kg and higher cause acute lethality in many mice. Iv doses cause acute lethality in mice more frequently than ip doses, which suggests a peak toxic effect. However, iv infusions in mice, which also can be curative to colon 38, can also result in a lethal effect, although more delayed, even though the predicted plasma concentrations are much below the peak plasma concentrations that appear to be necessary for acute lethality. Plasma concentrations, 100 to 600 μg/ml predicted to result from single doses that are therapeutic and not acutely lethal in mice, if maintained by infusion in dogs for 28 hours or longer result in delayed lethality. We conclude that relatively high plasma concentrations (> 100 μg/ml) are needed for therapeutic activity with this antitumor agent and that lethality can result from two distinctly different causes. An acute lethality can result from an excessively high peak plasma concentration (> 600 μg/ml). A delayed lethality can result from a too-long exposure (> 24 hrs) at therapeutically effective plasma concentrations (100–600 μg/ml). We also note that unexpected kinetic differences exist among the mouse, dog, and man. Whereas usually with antitumor agents plasma clearances are proportional to body surface area, and hence faster in small species, quite the opposite is true with flavone acetic acid. Mice exhibit a slower plasma clearance relative to dogs and man. [Cancer Treat Rep 70:1415–1421, 1986]

Flavone acetic acid (FAA) and FAA ester (fig 1) were selected for development by the Developmental Therapeutics Program (DTP) of the National Cancer Institute (NCI). The ester was selected because of its activity in DTP's P388 leukemia screen. FAA was subsequently selected through an analogue development process using as a guide the colon 38 murine solid tumor in which FAA ester demonstrated excellent activity. This colon 38 tumor is resistant to most clinically effective antitumor agents. Additional tests indicated that FAA demonstrated poor activity in the P388 and L1210 murine leukemias, but excellent curative activity in colon 38 and other murine solid tumors (1,2). Early screening tests with murine tumors showed that the ester was toxic to mice when administered iv at one-fifth the tolerated ip dose. With the acid, mice were able to tolerate equivalent doses by ip and iv routes of administration. When this finding is considered with a comparison of the structures of these two compounds, a logical explanation for these different ip and iv activities may be offered. The diethylaminoethyl moiety of the ester confers a procaine-like character to the ester (fig 1). Procaine is known to affect the heart when given iv. Independent testing of the ester has shown that hypotension clinically and cardiotoxic effects preclinically are manifested with the ester. In contrast to the ester, the acid has not shown cardiotoxic effects preclinically. The investigators who conducted these tests have also suggested that the ester is the prodrug for the acid, since after an ip dose of the ester to mice only the acid was

[1] Received Dec 20, 1985; revised Aug 11, 1986; accepted Aug 20, 1986.
[2] Presented in part at the 77th Annual Meeting of the American Association for Cancer Research, Los Angeles, CA, May 1986.
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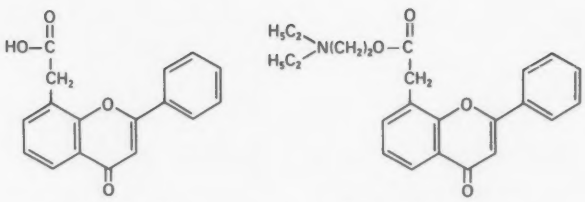
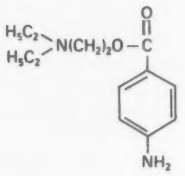


Flavone acetic acid
NSC 347512
LM 975

Flavone acetic acid ester
NSC 293015
LM 985



Procaine

FIGURE 1.—Structural formulas of 2 flavones and procaine. NSC refers to the NCI identification number. LM refers to the Lipha companies identification number.

measurable in the plasma (S. Kaye, and D. Kerr, personal communication). In human studies, when the ester was administered as a 1-hour iv infusion, the metabolically resultant acid measured in the plasma was higher in concentration than the ester and was cleared slower, t½ acid, 2 hours, t½ ester, 0.85 hour (3).

Taken as a whole, the picture from the studies described above suggests that FAA should be the current analogue to develop further as a clinically potential agent against solid tumors. In this manuscript, we relate and interpret data available from investigations to date concerning experimental therapeutics, toxicology, pharmacokinetics, and pharmaceutics of FAA. A recent review described some of the interesting pharmacological properties of flavones (4).

SOURCES OF INFORMATION

Most of the data reviewed and presented in this manuscript are from work done by contractors for the DTP of the NCI. Contractors were Battelle Columbus Laboratories and Midwest Research Institute (NCI contract CM-17365, Division of Cancer Treatment), Southern Research Institute (contract CM-47580), and the University of Iowa (contract CM-37561). Other data have come from interested independent investigators (Dr. T. Corbett, Michigan Research Foundation; Drs. S. Kaye and D. Kerr, University of Glasgow, Scotland). These noncontract investigators are publishing independently some of these data elsewhere (1,3). This manuscript is intended as the first attempt to interrelate many kinds of different preclinical data that are usually published separately. We hope to present a conceptual approach that might be useful to further clinical development of this agent.

METHODS

The determination of FAA in plasma was by high-performance liquid chromatography (HPLC) with a Waters μBondapak C18 column (300 × 3.9 mm ID) and a 3-cm Brownlee octadecyl guard cartridge. The mobile phase consisted of water, methanol, and acetic acid (50:50:2, vol:vol:vol), and the flow rate was 2.0 ml/min. Detection was at 254 nm and peak areas were electronically integrated with a Nelson analytical model 4400 data system.

Plasma samples were added to twice the volume of acetonitrile containing the internal standard, 4-phenylbutyric acid, and mixed by vortex for 30 seconds. A mixture of sodium chloride and sodium bisulfite monohydrate (4:1) was added (0.2 g/0.25 ml of plasma) and the mixture vortexed for 1 minute and centrifuged for a few minutes. The upper aqueous layer was aspirated and evaporated to dryness. Sodium hydroxide (0.1 N) was added to dissolve the residue. This dissolution was aided by sonication, and the solution was injected into the HPLC. The sensitivity of this method permitted detection of 0.4 to 1.1 μg/ml of plasma FAA as a lower limit. Interfering plasma indigenous peaks prevented further sensitivity. Extraction efficiency was between 96% and 102% (contract CM-17365).

RESULTS

Therapeutics and Pharmacokinetics in Mice

Therapeutic data are currently available from a number of drug administration schedules, both bolus and infusion, over a range of doses that spanned toxic, therapeutic, and nontherapeutic effects (1,2). Therapeutic and

toxic data in mice are related to predicted pharmacokinetic data.

Figure 2A illustrates some actual pharmacokinetic data from mice at two iv bolus doses, 200 mg/kg and 50 mg/kg, and also a pharmacokinetically predicted result from repetitive doses along with the reported therapeutic and toxic results. It appears from these data and the data from the dog illustrated in figure 3 that dose-dependent kinetics exists. For this reason, and because the optimal therapeutic dose in mice was 267 mg/kg (2), we chose as the best estimate of pharmacokinetic parameters for predictive use a 200 mg/kg dose in mice. By choosing these parameters for predicting expected plasma concentrations for the doses, both bolus and infusion, used in murine therapeutic experiments already conducted, we would be on the conservative side for our predictions of desirable plasma concentrations for therapy and of maximal plasma concentrations to avoid lethal toxicity. However, it is important to remember that these are only predictions from the best available data and higher plasma concentrations than those predicted are possible because of the dose-dependent nature of the kinetics.

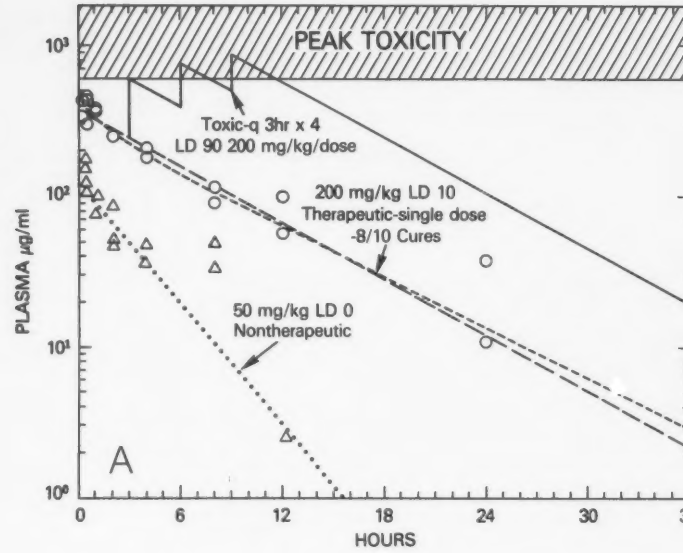
Through a review of therapeutic screening data and toxicity data available to us from several contractors, we conclude that FAA, when given as a bolus dose, exhibits a peak plasma toxic effect manifested as acute lethality. This conclusion is reinforced by data which show that iv bolus doses are more frequently toxic than equal ip bolus doses (2). Predicted plasma concentrations in mice illustrated in figures 2A and 2B indicate that this acute lethality occurs at brief exposures to plasma concentrations > 600 μg/ml in mice.

In figure 2B, note the LD80 at a single dose of 356 mg/kg, at which there was only a brief exposure to plasma concentrations > 600 μg/ml. Figure 2A illustrates the LD90 at a 200 mg/kg/dose which was not toxic as a single dose but which became acutely lethal with four repetitive doses at 3-hour intervals. It can be seen that plasma kinetic predictions indicate this dosing interval would cause peak concentrations to increase > 600 μg/ml.

In figure 2C we predicted plasma concentrations from infusion rates used in the therapeutic infusion studies conducted by Corbett et al (1). It is interesting to note that lethal toxicity occurred at plasma concentrations much less than the estimated peak plasma lethal toxic concentrations illustrated in figures 2A and 2B. These predicted plasma concentrations in figure 2 illustrate several points that we would like to emphasize. Lethal toxicity in mice can result from a brief exposure to a plasma concentration > 600 μg/ml, but also can result from a sustained plasma concentration in the therapeutically desirable range of 100–600 μg/ml if the exposure is prolonged as illustrated in figure 2C. The projected dose response curve is relatively steep. A small rise in plasma concentration may have a lethal effect; this can be seen by comparing plasma concentrations at the doses of 356 mg/kg and 267 mg/kg in figure 2B. Also, an increase in exposure time at therapeutically effective plasma concentrations may have a lethal effect as illustrated in figure 2C. The parameter that is still ill defined with the data currently available is the optimal time of exposure. Careful consideration of the predicted plasma kinetics in figures 2B and 2C along with some in vitro data do provide some hints (M. Lieber, personal communication). In vitro studies with renal carcinoma in a human tumor colony-forming assay where the FAA is constantly exposed to the cells for 7 days indicate that a threshold concentration of 100 μg/ml is needed to achieve cytotoxicity. From the predicted plasma data in figures 2B and 2C, one would conclude that this threshold of 100 μg/ml is not unreasonable as a first estimate for a threshold in vivo. In figure 2B, if we consider the plasma concentration of 100 μg/ml as a threshold and project to the abscissa, we see that an exposure of approximately 5 hours above this concentration resulting from a dose of 112 mg/kg is poorly therapeutic, whereas an exposure of approximately 10 hours above this concentration resulting from a dose of 267 mg/kg is highly therapeutic. The dose of 356 mg/kg is lethally toxic probably because of the peak plasma concentration achieved. In figure 2C, if we consider 100 μg/ml as a threshold, we see that at the lowest infusion rate of 10.8 mg/kg/hour, a total of 14 hours of exposure above threshold results in poor therapy and at 18.1 mg/kg/hour, a total of 25 hours of exposure above threshold results in excellent therapy, whereas at 25.3 mg/kg/hour, the resulting 29 hours of exposure above threshold was often lethally toxic to mice. These projections indicate that the time of exposure above a threshold alone cannot be the sole determinant for therapy; eg, 10 hours of exposure is highly therapeutic after a single dose of 267 mg/kg, whereas 14 hours of exposure is poorly therapeutic after an infusion of 10.8 mg/kg/hour. This indicates that some combination of exposure time and concentration above a threshold is important. We would suggest that the area under the curve (AUC) above a threshold may be a concept to consider in the further development of this drug.

Toxicity and Pharmacokinetics in Dogs

A feature that emerged from preclinical toxicology studies in beagle dogs is the lack of any unusual toxicity with single doses until very high drug concentrations are reached in the plasma. Figure 3 illustrates the plasma kinetics after several single iv doses and indicates dose-dependent pharmacokinetic behavior similar to that seen in mice. The dog whose plasma concentrations reached 900 μg/ml, after a single dose of 600 mg/kg infused over 30 minutes, became transiently sedated while the plasma concentration of FAA hovered between 700 and 900 μg/ml for 3 hours. However, this dog recovered from the sedation and survived with no unusual toxic symptoms. Four dogs at lower doses of 200 mg/kg and 50 mg/kg showed no unusual toxic symptoms. Plasma concentrations within the therapeutic window (100–600 μg/ml), as defined in previous thera-


PEAK TOXICITY
Toxic-q 3hr x 4
LD 90 200 mg/kg/dose
200 mg/kg LD 10
Therapeutic-single dose
-8/10 Cures
50 mg/kg LD 0
Nontherapeutic
PLASMA µg/ml
10^3
10^2
10^1
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A
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6
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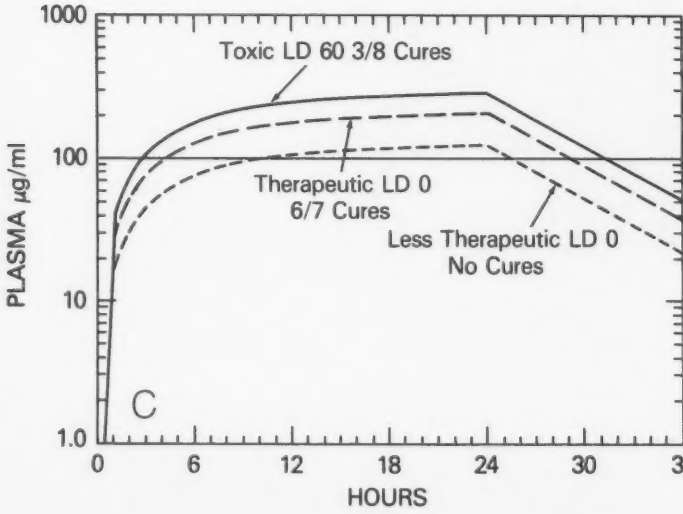
HOURS


Toxic LD 60 3/8 Cures
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6/7 Cures
Less Therapeutic LD 0
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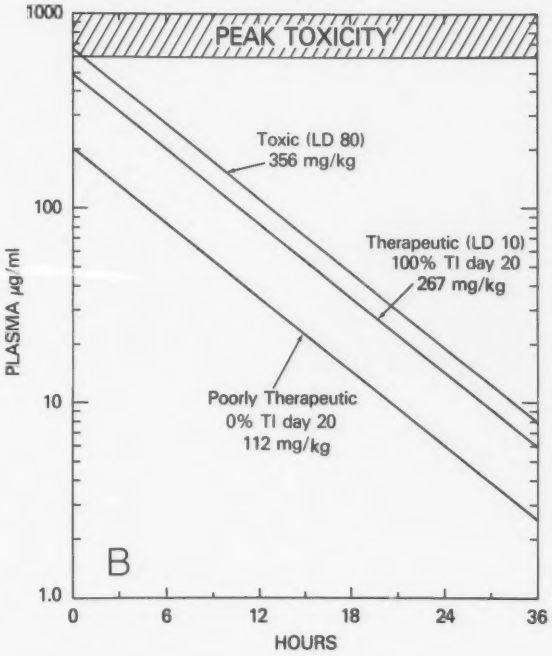

FIGURE 2.—Therapeutic and toxic doses of FAA in mice from detailed data reported in references 1 and 2. Plasma pharmacokinetics were predicted using the pharmacokinetic parameters calculated from data in mice at the dose of 200 mg/kg. 2A—Data in mice are illustrated at 200 mg/kg and 50 mg/kg (contract CM-17365). Each symbol represents the plasma concentration in an individual mouse given an iv dose of FAA. At 200 mg/kg, $t_{1/2} = 4.85$ hr, $V_D = 0.54$ L/kg, and $C_t = 368\ e^{-0.143t}$ with a correlation coefficient of 0.88. The long-dashed line is the fit with the least-squares program MLAB (9). The short-dashed line is a forced biexponential fit in which the parameters in the first phase had standard errors > 100% so as to make this fit undesirable with the current data. At 50 mg/kg, $t_{1/2} = 2.24$ hrs, $V_D = 0.36$ L/kg, and $C_t = 139\ e^{-0.039t}$ with a correlation coefficient of 0.78 (least-squares fit is the dotted line). The solid saw-toothed line is a predicted line for multiple doses at 200 mg/kg given every 3 hrs. 2B—The solid lines represent predicted plasma concentrations at the toxic and therapeutic iv doses indicated. 2C—Plasma predictions of FAA concentrations for reported (1) toxic and therapeutic infusions of FAA; infusion rates were 25.3, 18.1, and 10.8 mg/kg/hr for 24 hrs. The solid horizontal line at 100 µg/ml is for reference purposes to a projected threshold concentration.

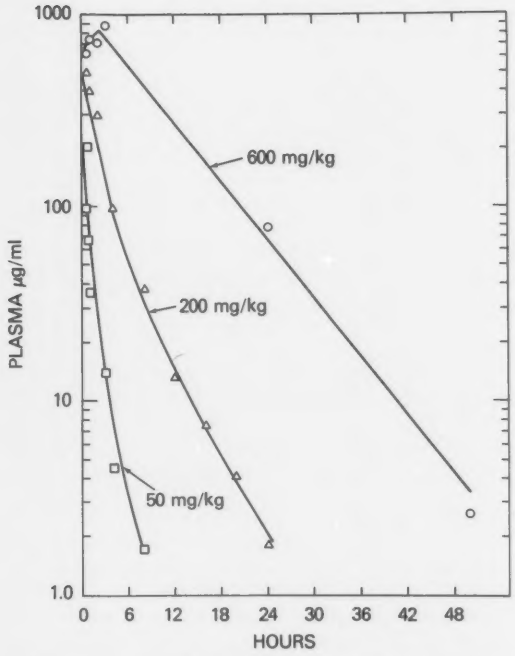

FIGURE 3.—Data illustrating the plasma kinetics of FAA in 3 dogs each receiving short iv infusions. Each symbol represents a separate dog at a different dose: ○ = 30-min infusion; △ = 12-min infusion; and □ = 3-min infusion (contract CM-17365). The 200-mg/kg dose was fit by least squares (MLAB) to a biexponential equation $C_t = 674\ e^{-0.78t} + 76\ e^{-0.14t}$ with a correlation coefficient of 0.89.

peutic and pharmacokinetic studies in mice, when prolonged by continuous infusions in dogs, did cause lethality in two dogs as illustrated in figure 4. Three dogs tolerated high sustained concentrations (between 100 and 700 µg/ml in plasma) for approximately 14 hours. Such a course of treatment can be repeated once a week for 3 weeks with no unusual signs of toxicity. However, one course of infusion for 56 hours, in which the plasma concentration did not exceed 200 µg/ml, resulted in toxic signs of sedation, gastrointestinal distress, and transient peripheral neuropathy. The dog eventually died 2 days later. Another course of infusion, which resulted in plasma concentrations as high as 430 µg/ml when the infusion was terminated at 28 hours because of sedation signs, also resulted in eventual lethality. There appears to be a threshold plasma concentration > 100 µg/ml for therapeutic activity in mice, and all the toxicity studies in dogs were conducted at close to or above this plasma concentration of FAA. These studies in dogs indicated that the time of exposure was critical in determining toxicity—a high (426 µg/ml) mean plasma steady-state concentration was not tolerated for a relatively short time (28 hrs); a lower mean plasma steady-state concentration (178 µg/ml) was not tolerated for a longer time (56 hrs). However, very high sustained concentrations ranging from 100 to 700 µg/ml were tolerated by dogs if the exposure time was limited to 14 hours.

PHARMACEUTICAL CHARACTERISTICS OF FAA

FAA is essentially insoluble (about 6 µg/ml) in water, but readily soluble at pH values ≥ 7. Concentrations of at least 25 mg/ml are obtained at pH 7–9. Stability of FAA was examined over a pH range of 7–11 at 70°C for up to 12 hours. Up to pH 9.6 there was no change; at pH 11.0, $t_{1/2}$ = 4.7 hours, and at pH 11.2, $t_{1/2}$ = 2.4 hours. Decomposition was noted only at pH > 10.5. Presently, FAA is formulated as a freeze-dried dosage form containing 250 mg of drug and sufficient sodium hydroxide to yield the monosodium salt. When constituted with 10 ml of sterile water for injection, USP, the resulting solution contains 25 mg/ml of FAA at pH 7.5. More concentrated solutions can be obtained by dilution with 2.4 and 4.8 ml of sterile water for injection to yield 100 and 50 mg/ml concentrations. These concentrated solutions are chemically and physically stable for 24 hours, but may precipitate when stored at refrigeration temperatures.

The reconstituted FAA solution may be diluted for infusion with 0.9% sodium chloride injection, USP (normal saline). Dilution with 5% dextrose to the same concentration results in a precipitate, presumably due to the lower pH of 5% dextrose injection. Prior addition of sodium bicarbonate (4 mEq/100 ml of 5% dextrose injection) prevented the precipitation and did not influence stability.

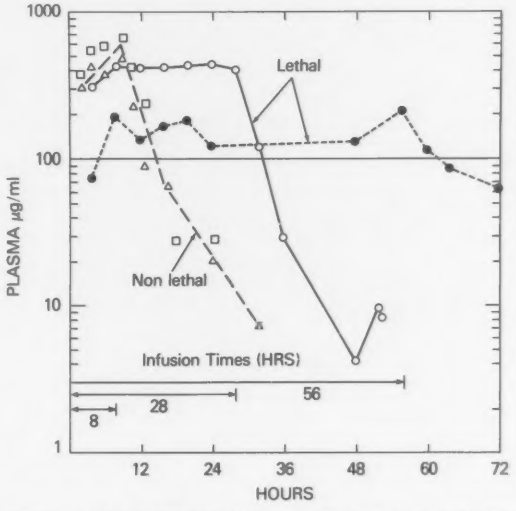

FIGURE 4.—Data illustrating plasma kinetics of FAA in beagle dogs receiving long-term iv infusions; ○ = 62.2 mg/kg/hr for 28 hrs; ● = 33.2 mg/kg/hr for 56 hrs; □ and △ = 125 mg/kg/hr for 8 hrs. Each symbol type represents serial samples from an individual dog. Data from contract CM-17365.

FAA is stable for at least 1 week as a reconstituted solution, and after further dilution with either normal saline or alkalinized (NaHCO3) 5% dextrose. However, the NCI formulation does not contain antibacterial preservatives and should be used within 8 hours of preparation.

The freeze-dried powder is also stable for at least 6 months at 50°C, room, or refrigeration temperatures (contract CM-37561).

An important point to consider is the relative insolubility of FAA at neutral and acid pH's. This could present a potential toxic kidney crystallization phenomenon at the high doses at which this agent will likely be used. A precedent for such a reaction exists clinically with methotrexate (MTX) (5–7).

This toxicity is prevented by hydration and alkalinization of the patients on high-dose MTX therapy. FAA is also quite soluble as the sodium salt at higher pH and alkalinization and hydration of patients on high-dose therapy with FAA should be considered.

DISCUSSION

FAA is an interesting investigational antitumor agent because of its demonstrated activity in murine solid tumors in vivo. Preclinical therapeutic studies in mice have indicated, with an advanced colon 38 tumor, that at optimal doses, a single dose was better than five consecutive daily doses, which in turn were better than nine consecutive daily doses (2). These findings suggest that prolonged exposure may be detrimental to therapy and that widely spaced intermittent exposure may be more therapeutic. Twenty-four-hour iv infusions in mice indicated that plasma concentrations between 100 and 200 μg/ml were also as effective therapeutically as single intermittent doses. However, plasma concentrations > 200 μg/ml that could be tolerated for a short time (5 hrs, fig 2B) could not be tolerated for a longer time (19 hrs, fig 2C).

We have introduced the concept of a therapeutic window for this agent because of observations in therapeutic experiments in mice and toxicity studies in dogs related to projected pharmacokinetic behavior in these species. We want to emphasize two important concepts derived from these comparisons. First, a very high plasma concentration (> 600 μg/ml) can cause immediate death in mice. Second, at concentrations (100–600 μg/ml) which are effectively therapeutic in mice, exposure times of 24 hours or longer can lead to delayed lethal toxicity in both mice and beagle dogs. Whether the AUC is an important factor to relate to therapeutic and toxic effects in vivo is yet to be determined. However, our initial analysis with limited pharmacokinetic data would suggest that AUC above a threshold concentration may be an important concept to consider. Usually agents in this molecular weight range (280 g/mol) are cleared more rapidly in small animal species (mice) than in the larger species (dog and man), since clearance is generally related to body surface area (8). FAA is unusual in this respect; at 200 mg/kg (600 mg/m^2) mice clear this drug less rapidly (240 ml/hr/m^2) than expected relative to dogs (2860 ml/hr/m^2). Man, at a dose of 1000 mg/m^2, has a reported clearance on the average of 6000 ml/hour/m^2 (S. Kaye and L. Malspeis, personal communications).

The half-lives are approximately: mice, 2–5 hours; dogs, 5 hours; and man, 2 hours (contracts CM-47580 and CM-17365; ref 3). This characteristic posed some problems in early therapeutic studies in mice where frequent (3 hrs) repetitive doses most likely resulted in acute lethality because of rising peak plasma concentrations after each dose, whereby the plasma peaks rose to intolerable plasma concentrations (fig 2B).

One observation worthy of emphasis is that sedation occurs in mice with therapeutically effective nonlethal regimens and that escalation to the next higher dose of the regimen once sedation has been observed is frequently lethal.

Direct extrapolation of schedules from mice to man after short duration administrations may be misleading. Consider the following: if a 600-μg/ml concentration in mice is achieved with a short infusion (1 hr) and the $t_{1/2}$ is 5 hours, it will take 13 hours before the plasma concentration is < 100 μg/ml or out of the anticipated therapeutic window. In contrast, if the same initial concentration of 600 μg/ml is achieved in man with a 1-hour infusion and the $t_{1/2}$ is 2 hours, it will take only 5 hours before the plasma concentration is < 100 μg/ml and the exposure time at therapeutic concentrations would be in man about one-half that in mice after one course of treatment. This difference in exposure time could lead to ineffective therapy. Optimal therapy with this agent should consider the different kinetic characteristics across species as well as relative doses or total amount of drug administered.

We have presented some concepts derived from preclinical studies with this unusual but interesting agent that might be useful in preclinical and clinical studies. Although we have given concentrations and exposure times for therapeutic and toxic effects, there is no guarantee that such concentrations or exposure times are directly extrapolatable to studies in man. Early clinical trials with this agent do indicate that high initial plasma concentrations are achievable in man, but that plasma protein binding is higher than in preclinical species.[4] However, we believe the concepts derived in such preclinical species are likely to apply to clinical use of this agent.

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Performance Status Assessment Among Oncology Patients: A Review[1]

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Performance status is a global assessment of a patient's ability for self-care and ambulation. It is an important and widely used prognostic variable for patients with cancer. Several different scales to assess performance status are in use, and scale scores are used for a variety of purposes, including patient selection and stratification for cancer clinical trials. New uses for life quality evaluations have also been proposed. Despite the widespread use of the scales, little information is available about the reliability and validity of these measures. Improved and extended application of these scales requires that several types of data about measurement properties of the scales be collected and analyzed. Various issues related to the measurement properties of the scales and their implications for oncology need to be understood to best develop their use. [Cancer Treat Rep 70:1423–1429, 1986]

Performance status is a global assessment of a patient's ability for self-care and ambulation. It has been demonstrated to be an important prognostic factor for patients with a wide variety of cancers (1–15). Review of treatment data has shown that performance status must be considered in the design and analysis of nearly all clinical trials in cancer treatment. Thus, there have arisen several scales for performance status assessment, and these have been applied rather widely in oncology practice and research. Despite the importance and widespread use of the measures of performance status, little information is available about several crucial measurement properties of the scales of performance status.

Measurement of "performance status" among cancer patients was initiated in 1948 with the introduction by Karnofsky of a ten-point scale which now bears his name (16) (table 1). Performance status, as originally conceptualized, was a scale to assess a patient's functional capabilities (for self-care, daily activities, and work).

This ten-point scale remains in use. However, in order to simplify and presumably to make assessment more usable and reliable, many modifications of this scale have appeared. Most of the newer scales tend to be abbreviated versions which collapse the ten-point scale to five-, four-, or two-level assessments (12,17) (tables 2 and 3). Other scales have also appeared which have a somewhat different approach to the assessment of performance. The "new" versions of performance assessment were introduced without an overall assessment of the measurement properties of the scales, and no overall evaluation of the application of any of the various scales has yet appeared. Some of the more widely used measures of performance status are shown in tables 1-3. This review will discuss the need for the evaluation of performance status scales, and will focus upon those aspects of these scales which might be used to assess the measurement (ie, validity and reliability) properties of the scales.

Uses of Performance Status Assessment

Following its introduction in 1948, performance status assessment has become widely used in oncology research and practice basically for three reasons.

(*a*) Performance status is a major prognostic factor for patients with lung cancer and other tumors (1–15) independent of treatment;

(*b*) Performance status is a predictor of toxicity and may also be an indicator of comorbid disease (2) or other "host factors";

(*c*) Patients with diminished performance status, as a rule, are less likely to benefit from treatment as compared to patients with higher levels of performance status (2).

The use of performance status measures in oncology research and practice has been extremely successful,

[1] Received Nov 27, 1984; revised Aug 4, 1986; accepted Aug 19, 1986.

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[3] S. T. Orr was supported by a special fellowship of the Leukemia Society of America while much of this work was conducted.

[4] We thank the anonymous reviewers for their helpful comments concerning this manuscript, and Margaret Gallagher for manuscript preparation.

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TABLE 1.—Karnofsky scale of performance status*

	Condition	%	Comments
A.	Able to carry on normal activity and to work. No special care is needed.	100	Normal. No complaints. No evidence of disease.
		90	Able to carry on normal activity. Minor signs or symptoms of disease.
		80	Normal activity with effort. Some signs or symptoms of disease.
B.	Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
		60	Requires occasional assistance, but is able to care for most of his needs.
		50	Requires considerable assistance and frequent medical care.
C.	Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled. Requires special care and assistance.
		30	Severely disabled. Hospitalization is indicated although death is not imminent.
		20	Hospitalization necessary. Very sick, active supportive treatment necessary.
		0	Dead.

*Source: ref 16.

and these measures have been widely accepted and employed. Applications of these scales of performance status have focused upon the following purposes.

(*a*) *To select patients for inclusion in treatment trials such as chemotherapy, radiotherapy, and other treatments.* Many protocols, particularly those of the collaborative groups, explicitly state performance status levels for inclusion or exclusion eligibility in the study. Furthermore, even when performance status criteria for patient inclusion/exclusion are not explicit, such criteria are generally implicit and derived from training and education. Recent reports have suggested that some (aggressive) treatments should be applied only to patients of certain levels of performance status (18). It then becomes intuitively obvious that considerable discrepancy among performance status raters will result in some eligible patients being excluded from potentially effective therapy and, conversely, some patients being included who might be more susceptible to toxicity.

(*b*) *To stratify patients on the basis of performance status evaluation at the beginning of a clinical trial.* Given that performance status is important in predicting outcome (survival, response, toxicity, etc), balancing this factor reduces the possibility of extraneous bias due to differences in functional status between experimental and control groups. This also permits treatment effects to be evaluated within homogeneous strata, ie, within groups of similar performance status. Again, inter-rater variability may produce an imbalance of this factor, introducing error into the analysis.

(*c*) *To measure the efficacy of treatment.* Improvement of performance status following treatment is sometimes utilized as an indication of improvement in health status (ie, a desirable effect), while decline is sometimes interpreted as a deterioration in health status (ie, an undesirable effect). A recent paper noted that changes in performance status associated with treatment should be reported with the other results of clinical trials to help evaluate the potential efficacy of therapy (19). Inter-rater variability could, of course, confuse such assessments.

(*d*) *To measure the "quality of survival" of cancer patients.* This is the most recent use of measures of performance status. Conceptually, quality of survival is related to efficacy measurement as stated above, but extends evaluation to potentially include many aspects of functioning. The time from treatment to deterioration in performance status has been used (20) as an indicator

TABLE 2.—Cancer and Leukemia Group B (CALGB) scale of performance status*

Value	Description
0	Ambulatory without symptoms
1	Ambulatory with symptoms
2	Bedridden < 50% of daytime
3	Bedridden > 50% of daytime
4	Totally bedridden

*Source: ref 13.

TABLE 3.—Eastern Cooperative Oncology Group (ECOG) scale of performance status*

Value	Description
0	Normal activity
1	Symptoms, but nearly fully ambulatory
2	Some bed time, but needs to be in bed < 50% of time
3	Bedridden > 50% of daytime
4	Totally bedridden

*Source: ref 17.

of the duration of the "good quality" survival of cancer patients. While performance status may be a measure of functional status, it is not a measure of "quality of life," since quality of life measures ordinarily contain an assessment of satisfaction with life (21) as well as other constructs such as psychologic function or social interaction not contained in performance status scales. Furthermore, it is unclear to what extent performance status scores are correlated with scores on measures of functional status.

Performance status measurement is therefore of critical importance in all oncology specialities for clinical decision-making (patient selection), data analysis (stratifying patients to create similar experimental and control groups), and outcome evaluation.

Of the various scales, the Karnofsky scale is a more global assessment of functional ability than the others, since it measures the ability to perform work and self-care activities as well as symptom status. However, the rating items can be relatively subjective. To overcome some of the subjectivity, several recent reports have suggested that laboratory parameters such as the level of lactic dehydrogenase, wbc count, hemoglobin, albumin, etc, might prove to be better predictors of patient outcome (ie, prognostic factors) than measures of performance status, because laboratory parameters are potentially less subjective ratings (22). However, laboratory values may not be preferable to performance status assessments because:

(*a*) They have not been shown to measure the same parameters;

(*b*) They do not provide any measure of function;

(*c*) They are more costly and time-consuming to obtain;

(*d*) They lack the uniform acceptance and demonstrated statistical importance of the performance status data.

Thus, rather than replace performance status assessment with another system which measures different parameters, it is more appropriate to define the uses and limitations of the performance status scales and identify the problems inherent in their application. The complementary combined use of multiple rating systems (ie, lab values plus performance status) may offer even greater prognostic information.

Measurement Issues With Performance Status Assessment

The successful application of performance status is critically dependent upon basic measurement properties of the instruments, namely validity and reliability.

Validity

"Validity" refers to what may appropriately be inferred from scores on a measurement tool (23). In order to evaluate the validity of an instrument, it is necessary to inquire into the nature or meaning of the variable(s) being studied (24). Typically, there is an attempt to ascertain if the individual items on the instrument, taken together, provided an accurate assessment of the variable purportedly being measured. For example, with the Karnofsky scale, the basic validity issue could be stated: "Does the Karnofsky performance status scale accurately measure patient functional status?" or "Can differences between patients in Karnofsky scores be interpreted as true differences in functional status, or can these differences be explained by other properties?" Validity assessment can be divided into several different subtypes of evaluation, including: face validity, content validity, criterion-related validity (both concurrent and predictive), and construct validity.

Face validity is probably the least scientific of the inquiries into validity of the various measures, and involves a nonempirical judgement by potential users of the instrument (not necessarily experts in measurement) that the items on the instrument appear to be relevant as measures of the variable of interest (eg, that fever, redness, swelling, and pain appear to be relevant variables to consider to determine presence of infection). This is in contrast to *content validity* assessment, in which a judgment is made of the representativeness of the content of the items of the construct (ie, functional capacity) being measured. This requires that a thorough and detailed definition of the objectives of the measure and the variable purportedly being measured be developed, so that items can be systematically evaluated vis-a-vis these definitions. For example, with the performance status scales, if the variable being studied were functional status or capacity, then the evaluations should contain measures of capacity to perform activities of daily living, work, and self-care. One would thus assess the Karnofsky or other performance status scales (nonempirically) for the items that evaluate areas which have been defined as encompassing functional status.

Criterion-related validity refers to the extent to which scores on the instrument being studied (eg, Karnofsky) are associated with the patient's most likely "score" on another variable, called a "criterion" (23) (eg, a low performance status score would be expected to be associated with decreased survival). When the criterion variable is assessed concurrently with the measure being studied, the assessment is called *concurrent validity.* When the criterion variable is assessed at some point in the future, the assessment is called *predictive validity.* These assessments of criterion-related validity provide important practical information about the ability of a measure to diagnose a problem or to predict an outcome (23,24). Predictive validity is an assessment of the ability of a test to predict a future outcome. It does not provide information defining the nature of the construct being measured (24). For example, the predictive validity of the performance status measures, when response to treatment or duration of response is used as the criterion variable, is very good. Mor et al (25) evaluated the predictive validity of the Karnofsky scale and found a significant ($r = 0.30$, $P < 0.001$) correlation between Karnofsky score at initial interview and longevity in a group of terminally ill cancer patients.

Which, if any, of the commonly used measures of performance status [ie, Karnofsky, ECOG, CALGB, Southwest Oncology Group (SWOG)] has better predictive ability is unclear. Stanley (4) has suggested that in lung cancer, collapsing the Karnofsky scale results in dramatic loss of prognostic information. Others advocating expanded scales also feel there is loss of information with smaller scales. Additionally, prior estimates of predictive ability of the scales of performance status may have been somewhat imprecise. This would be the case if multiple raters entering patients into single trials did not apply performance status ratings exactly in the same fashion. Absence of agreement between raters could create heterogeneous groups for analysis, and the estimates of predictive validity could therefore be inaccurate. More will be said about the problem of agreement between raters in the "Reliability" section below.

Construct validity is the assessment of what variable(s) might explain individual differences in scores on a measuring instrument. With the performance status scales, differences in scores between patients might be attributable to differences in functional capacity, or alternatively to differences in other variables such as socioeconomic status, depression, denial, beliefs about the efficacy of treatment, etc. Construct validation is not focused upon the practical utility of the measure, but rather upon a search for the meaning of test scores (24). Construct validity is thus evaluated based upon the results of multiple assessments of the instrument, through which information about the instrument can be accumulated (23,24). These multiple assessments are essentially tests of hypotheses concerning the characteristics of those with different scores on the test instrument (23). With performance status measures, for example, a statistically significant correlation between performance status scores and scores on a measure of functional capacity might be hypothesized. Likewise, one might hypothesize that performance status scores would not be correlated with scores on a measure of anxiety.

Three prior investigators have studied the construct validity of the Karnofsky scale of performance status by evaluating correlations of Karnofsky performance status scores with measures of functional ability, such as ability to perform activities of daily living. Mor et al (25) found a significant association between Karnofsky performance status scores and ability to perform activities of daily living such as walking, dressing, and bathing. Wood et al (26) compared Karnofsky performance status scores to scores on physical therapy assessments of ambulation, activity, and time out of bed. These authors reported significant correlations between Karnofsky performance status scores and these measures of functioning. Finally, Schag et al (27) similarly found significant correlations between Karnofsky performance status scores and the measures of self-care, daily activity and ability to work, and evidence of disease. Similar data do not exist for other performance status measures.

Through the mechanisms of content, criterion-related, and construct validity, one learns what may accurately be inferred from scores on a measurement tool. With the performance status scales, little such information is available. While performance status scores at the time of diagnosis predict certain measures of patient outcome, it is unclear exactly what "performance status" measures. Until research into the meaning of performance status scores is conducted, it is not appropriate to use these scores as measures of therapeutic outcome or functional status, since they may in fact measure entirely different variables, such as depression or attitude toward therapy. However, because of their widespread use, acceptance among clinicians, and ease of obtaining scores, performance status measures may be a mechanism to provide information, in part, about functional capacity, and in particular, as a measure of therapeutic outcome. Considering the multitude of therapeutic options, in some cases where there is a need to choose between toxic therapies or to choose between marginal therapies, an assessment of potential outcome can have a tremendous impact on treatment choices and professional guidance. Thus, measures of outcome for patients with cancer are desperately needed. Research about the validity of the scales of performance status may provide a basis for using these measures to assess functional capacity as one measure of outcome among oncology patients.

Reliability

Reliability is the accuracy of a measuring instrument (24), where accuracy refers to the stability, dependability, or consistency of test scores (eg, between and among raters) (23,24). Reliability evaluation may involve many types of assessments, including internal consistency, temporal stability, and inter- and intra-rater variation. The types of assessments used depend upon the structure and uses of the measurement tool and the type of error being sought.

Since all performance status scales are single item, measures of internal consistency between items are not feasible. Also, since performance status may change from one test administration to the next, due to treatment effects (response or toxic effects) or disease progression, temporal stability of performance status scores would be difficult to assess. Therefore, reliability assessment for performance status is primarily concerned with intra- and inter-observer reliability or agreement.

Intra-rater refers to the extent of agreement when one rater blindly and separately evaluates the same patient twice, while inter-rater agreement refers to the agreement between two or more raters who independently and blindly evaluate the same patient at approximately the same time. These assessments are important because consistency between raters (inter- or intra-rater) is assumed in the design of clinical trials in oncology. For example, performance status assessments are used to screen patients for inclusion in clinical trials and these eligibility criteria need to be uniformly applied if there are to be comparable experimental and control

groups with relatively homogeneous performance status categories. When there is considerable discrepancy among raters, then some eligible patients may be excluded, or conversely some patients may be incorrectly included who may be more susceptible to toxicity. Also, should the "experimental" group contain proportionately more patients of diminished performance status than the "control" group, treatment efficacy would be incorrectly underestimated. Conversely, if the control group contained proportionately more patients of diminished performance status than the experimental group, then treatment effect would be inaccurately overestimated. Similar potential problems exist with patient stratification. As a result, treatment effects might be incorrectly assessed if either the experimental or control group contained proportionately more patients of diminished performance status. Such variability may, in part, explain the tendency for cooperative groups to have lower response frequencies than the single-institution pilots on which the trials are based.

Intra-rater reliability has not been assessed in any prior studies. This is a very difficult evaluation which could probably best be accomplished through the use of video tapes, audio tapes, or completed patient questionnaires. Clinical assessment generally would be difficult for two reasons. First, if patients are evaluated over a short temporal interval, the rater may recall the first score, which would bias the second assessment. Second, if the temporal interval between assessments is lengthy, the variable being measured (performance status) could truly change, invalidating the reliability assessment. One approach to "blinding" the rater would be the use of a simple questionnaire concerning a patient's ability to perform activities of daily living. A single reviewer could assign a performance status score to the same questionnaire twice and agreement could be assessed.

Several prior studies have addressed the issue of inter-rater agreement in the assignment of Karnofsky performance status scores (data are not yet available about other scales). Yates and colleagues (28) evaluated inter-observer reliability of the Karnofsky scale between nurses and social workers and between clinic and home ratings. They found moderate degrees of inter-rater reliability ($r = 0.69$) between the nurses' and the social workers' ratings, using Pearson's product-moment correlation coefficient, which measures the extent of a linear association between two measures but not the absolute agreement between them. In this study, physician-physician agreement was not assessed.

Hutchinson et al (29) studied inter-physician variability in the use of the Karnofsky scale and found agreement between rater pairs to be relatively low, using a statistical approach based upon the extent of perfect agreement between rater pairs. Although suggestive of problems in the use of Karnofsky scales for routine oncology, their analysis was not done using patients with cancer. Their sample included chronic hemodialysis and emergency room patients. These patients have a different spectrum of medical problems and are cared for by a health care team which may have neither familiarity with nor commitment to the assessment of performance status.

Schag et al (27) evaluated agreement in the assessment of performance status between two sets of health care providers: physicians, "primarily oncologists;" and mental health professionals, "primarily a psychologist and psychiatrist who work with cancer patients on a regular basis." The physicians rated 75 patients using the Karnofsky scale after a medical visit, while the mental health professionals rated them after conducting an interview about their daily activities and physical functioning. Agreement as measured by Pearson's product-moment correlation coefficient was $r = 0.89$, indicating a relationship between ratings, although not necessarily perfect agreement on individual patients. Agreement as indicated by the Kappa statistic (a measure of agreement between rater pairs) produced a Kappa of 0.53 (values in the case of more agreement than that expected by chance alone range from 0 to 1). Complete agreement was observed for 59% of all patients rated. This study did not involve pairs of oncologists rating patients, leaving unanswered the crucial question about agreement between medical oncologists (the major users of performance status scales) or between individuals (such as chemotherapy nurses) who routinely evaluate treatment protocol eligibility.

In a prior study, using cancer patients, nonphysician interviewers were trained to use the performance status scales in order to achieve very high levels of inter-rater reliability (25). The training procedure consisted of providing operational definitions, based upon activities of daily living, for each performance status level of the Karnofsky scale. This study was done as part of the National Hospice Study, a nationwide evaluation of the impact of hospice care on the quality of life and health care costs of terminally ill cancer patients. As would be expected in a study of terminally ill patients, most of the patients involved in the hospice study were at the lower end of the Karnofsky scale. The nonphysician interviewers utilized the operational definitions to achieve excellent levels of inter-rater agreement [intraclass correlation coefficient of 0.97 (25), which is equivalent to a Kappa statistic of 0.97 (30)]. However, this paper did not answer either the question of inter-rater reliability or how to improve agreement between raters among physicians working in oncology practice and research settings. Since this is the setting in which the Karnofsky scale is most frequently utilized, it is imperative to address the issue of inter-rater agreement in this type of setting. This study does suggest, however, that specific training in the use of the scales can improve agreement.

Despite the accumulating information about performance status assessment, none of the prior studies cited above addresses the specific issue of physician-physician agreement in oncology settings. Performance status ratings made by oncologists are of particular importance,

since these ratings are used to determine patient eligibility for clinical trials as well as for purposes of stratification. While other health professionals use the performance status scales, the agreement between oncologists is of practical concern for the conduct and analysis of clinical trials in oncology. Further studies to determine reliability and evaluate the impact of training are very important to maximize the usefulness of these measures. The need for evaluating and possibly improving inter-observer reliability of performance status is now of particular importance. New treatments and combinations of treatments are being tested at an ever accelerating pace. In addition, there is considerable interest in enrolling patients to clinical trials from the busy office and community hospital setting through the Community Hospital Oncology Program (CHOP) and the Community Clinical Oncology Program (CCOP). Thus, increasing numbers of patients will need to have performance status rated for the purposes of determining eligibility for inclusion in treatments. It is therefore crucial to define intra- and inter-rater agreement among those who enter patients into trials, and, if necessary, to develop methods to improve these measures of reliability.

CONCLUSION

The recognition of pretreatment performance status as a clinical factor and the development of a scale to assess this prognostic factor were major steps in clinical oncology, allowing for a higher degree of discrimination between treatment options. Scales of performance status have been used extensively and successfully as methodologic, statistical, and clinical tools. However, data to evaluate the application of the tools and to possibly improve the current applications are not yet available.

A small number of prior studies have evaluated various aspects of the reliability and validity of the Karnofsky scale. No such evaluations exist for the other scales used to measure performance status (*see* tables 2 and 3), either singly or relative to other scales.

Until such time as additional evaluative data are available concerning the various scales used, it may be useful if the Karnofsky scale of performance status is more widely adopted for use. Data about the psychometric properties of this scale are available (although not extensive) and these data suggest that the scale has adequate inter-rater reliability as well as construct and predictive validity. Additionally, evidence is available that behaviorally based rating criteria can be developed to increase inter-rater agreement of users of the scale (25). Thus, consistent use of this scale between raters and institutions is possible. Use of the alternate scales should be considered based upon analyses of relevant psychometric data.

Obviously, the data needed to assess and compare the validity and reliability of the various scales will be expensive and time-consuming to collect and analyze. Each type of reliability and validity assessment is important, for each provides different yet complementary information. Adequate assessment of the performance status measures along the dimensions of reliability and validity may lead to improved application of the scales, and in turn to improved patient care through better patient selection, classification, and evaluation.

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BRIEF REPORTS

Neoadjuvant High-Dose Methotrexate, Cisplatin, and Doxorubicin for the Management of Patients With Nonmetastatic Osteosarcoma[1,2]

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Historically, the cure rate for patients with nonmetastatic osteosarcoma (OS) with ablative surgery and/or radiotherapy directed at local tumor control has been approximately 20% (1,2). However, with the introduction of chemotherapeutic regimens in conjunction with definitive surgery, disease-free survivals (DFS) of between 45% and 90% have been reported (3-7).

This report describes the Hospital for Joint Diseases/Orthopedic Institute—Mount Sinai Medical Center (HJDOI-MSMC) experience in patients with nonmetastatic OS. The objectives of this study were to initiate aggressive preoperative chemotherapy (CT) with high-dose methotrexate (HDMTX), doxorubicin (DRN), and cisplatin (DDP) immediately after biopsy, to perform limb salvage surgery whenever possible, and to improve survival.

PATIENTS AND METHODS

A total of 34 patients with biopsy proven high-grade central OS were evaluated between April 1982 and July 1985. Seven patients presented with pulmonary disease at the time of diagnosis and were excluded from the study. Two additional patients, who had disease recurrence and presently are without evidence of disease, were nonevaluable, one secondary to a major protocol violation and the second because pathologic review revealed a pleomorphic sarcoma.

Following an open biopsy of the primary tumor, the first 11 patients treated began from two to four 28-day cycles of preoperative CT with HDMTX, DDP, and DRN. The number of cycles was determined by the clinical response of the tumor to CT and the operative procedure to be performed. The subsequent 14 patients received two cycles of preoperative CT. After definitive surgery, the tumor response to preoperative CT was determined as described by Rosen et al (5).

HDMTX was administered on Days 0 and 7 of each cycle. The HDMTX was administered with vigorous hydration at a dosage of 8 g/m^2 for children $>$ 12 years old, and 12 g/m^2 for those $<$ 12 years old. The dose of MTX was escalated by 1 g/m^2 in subsequent courses until a peak level of 10^{-3} M was reached. Leucovorin, 20 mg/m^2/dose, was started 16 hours after the completion of the HDMTX. It was administered every 3 hours iv for eight doses, then every 6 hours orally for eight doses.

DRN was given at a dose of 25 mg/m^2 iv for three doses on Days 15, 16, and 17 of Cycles 1-7. The total DRN cumulative dose did not exceed 525 mg/m^2.

DDP was administered at a dose of 75 mg/m^2 iv on Day 15 of Cycles 1-7; for Cycles 8-10, the DDP was increased to 120 mg/m^2.

Hematopoietic, renal, and hepatic functions were monitored prior to each CT administration. Performance status, nutritional assessment, anthropometric measurements, audiometrics, and cardiac function were assessed at each odd-numbered cycle. An evaluation for metastatic disease and/or local recurrence was performed every 4 months during therapy, and for the first 2 years off treatment, and then at 6-month intervals for 2 years, and yearly thereafter.

Estimates of DFS and overall survival were determined by the Kaplan-Meier method. The analysis of patient characteristics associated with relapse was determined by Fisher's exact test (two-tailed). Due to the small sample size, prognostic factors were studied as a

[1] Received Dec 16, 1985; revised May 12, 1986; accepted July 15, 1986.
[2] Supported in part by The Tomorrows Children's Fund and The Chemotherapy Foundation, New York, NY.
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function of the discrete variable relapse rather than time to relapse (ie, DFS). The period of follow-up for individuals at each level of a prognostic factor was checked for comparability to ensure that this did not bias the results.

Informed consent was obtained from every patient prior to entry onto study.

RESULTS

Seventeen of 25 patients, ten with proximal lesions and seven with distal lesions, had a limb salvage procedure. One patient with a distal femoral OS developed an infection at the site of the prosthesis and ultimately required an amputation; thus, 16 of 25 patients (64%) had a successful limb salvage operation.

Pathologic material of the tumor specimens was available for review on 24 patients and revealed the following responses to preoperative CT: grade I, 0; grade II, 3; grade III, 7; and grade IV, 14.

The median follow-up period for the 20 patients still alive is 35.5 months with a range of 13–48 months. All patients have completed CT. Seven of 25 patients have had a recurrence of their disease, three while receiving CT, and one each at 18, 22, 25, and 33 months from the time of diagnosis. The site of relapse was pulmonary parenchyma in four patients, bone in two, and both sites in one. The estimated 2-year DFS and overall survival are $77\% \pm 0.19\%$ and $76\% \pm 0.19\%$, respectively. One patient died without evidence of disease confirmed by autopsy. This patient was counted as an "event" for survival purposes, but was censored at the time of death to calculate DFS.

Parameters analyzed and found to be of no prognostic significance with respect to disease recurrence included: race, age, sex, site of the primary tumor (distal vs proximal and femoral vs other), type of definitive surgery (amputation vs limb salvage), and the grade of the pathologic response to preoperative CT. Patients with a primary tumor > 9 cm had a nearly statistically significant increased risk of relapse ($P = 0.069$).

The chemotherapy regimen induced nausea and vomiting in all patients. Twenty-one of 25 patients required at least one delay in the treatment protocol of from 1 to 3 weeks, secondary to toxicity; and, in 15 patients, toxicity necessitated dosage modifications. The major toxic effects were neutropenia and thrombocytopenia. Ten patients required hospitalization for fever and neutropenia, and four needed platelet transfusions. Two patients experienced heightened, but self-limited, transaminasemia of > 1000 U, secondary to HDMTX. Two patients experienced delayed MTX excretion which necessitated prolonged iv hydration and increased dosages of leucovorin. Seven patients had a diminished cardiac ejection fraction, and although all were asymptomatic, DRN was discontinued at a cumulative dose level of 450 mg/m^2. Five patients had a significant weight loss, and three of the five lost $> 10\%$ of their baseline weight and required either nasogastric tube feedings or central hyperalimentation. Irreversible renal toxicity was not encountered in any patient.

DISCUSSION

This report details 25 patients with nonmetastatic, high-grade OS treated at the HJDOI-MSMC. All patients received from two to four cycles of preoperative CT. The response of the primary tumor to CT was graded histologically, and no difference could be ascertained whether two, three, or four preoperative cycles were administered. Regardless of the outcome, the identical CT was given to all patients postoperatively. Although 90% of the patients had grade III–IV histologic responses, five of the seven relapses occurred in this cohort; histologic grade of response did not predict outcome in this small series. The excellent response may be attributed to the administration of three drugs in every cycle.

Prognostic variables thought to predict survival include: sex, age, primary site, tumor size, pathologic type, duration of symptoms, type of surgery, extent of disease, and the histologic response to preoperative CT (5,8,9). In our series, only large tumor size approached significance in predicting outcome. Our inability to identify other factors may be due to our small patient population.

Our study yields an estimated 2-year DFS of $77\% \pm 0.19\%$ and an overall survival of $76\% \pm 0.19\%$. The CT regimen of HDMTX, DRN, and DDP was tolerated and no patient suffered any long-term or permanent morbidity. These results compare favorably with other reports in the literature and substantiate the need for CT in patients with OS.

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BRIEF REPORTS

In Vivo Synergy of Vitamin K_3 and Methotrexate in Tumor-Bearing Animals[1]

Joseph Gold[2,*]

In vivo synergy was demonstrated with vitamin K_3 (menadione) and methotrexate in rats bearing the Walker 256 im carcinosarcoma, without concomitant increase in toxicity. Synergy is defined as a combined antitumor effect which exceeds the sum of the individual antitumor effects. It is suggested that such synergy, extended to human neoplasms, may significantly increase the effectiveness of methotrexate as a chemotherapeutic agent. [Cancer Treat Rep 70:1433-1435, 1986]

Vitamin K_3 (menadione), a synthetic antihemorrhagic naphthoquinone, has long been known as a potential anticancer agent and radiosensitizer (1,2) following demonstration in the late 1940s of tumor necrosis in patients receiving menadiol sodium diphosphate (Synkavite) converted in vivo to menadione (3). More recently, vitamin K_3 has been found to inhibit the in vitro growth of murine L1210 leukemia in flask culture (4) and a variety of rodent and human cell lines in culture, including murine neuroblastoma, melanoma, and glioma (5), as well as a wide spectrum of human tumor explants in the soft agar (clonogenic) assay system (6). At the same time in vitro synergy has been demonstrated between vitamin K_3 and methotrexate or 5-fluorouracil in the L1210 liquid culture growth assay system (7,8). While human clinical trials have been initiated with a combination of vitamin K_3 and (warfarin and) 5-fluorouracil (6), no such trials, or any in vivo results whatsoever, have been reported with a combination of vitamin K_3 and methotrexate. Since methotrexate represents a chemotherapeutic agent of considerable clinical potential, the present study was undertaken to ascertain the effect of a combination of vitamin K_3 and methotrexate in a sensitive in vivo tumor screen.

MATERIALS AND METHODS

The Walker 256 im carcinosarcoma in female Sprague-Dawley descendant rats (approximately 100 g; Taconic Farms, Germantown, NY) was used as the in vivo tumor screen. Protocols employed conformed to those in general use (9) and were as follows. On Day 0, 5×10^6 cells (obtained from the ascites form of Walker 256) in a volume of 0.2 ml were inoculated into one thigh of a rat. On Days 3-6 (after development of a palpable tumor of 1-2 g), treatment was administered ip (milligram per kilogram of body weight per day). On Day 7, the animal was killed; both lower extremities were removed in an identical manner and the difference in weight between the tumor thigh and the contralateral thigh was inferred to be the weight of the tumor (correlation of about 1:1 with actual excision and weight of tumor). Ten animals were used in each test and control group. Percent tumor inhibition represented $(1.00 - T/C) \times 100$, where T/C was the ratio of the average tumor weight of the test animals divided by the average tumor weight of the control animals. Average weight change (AWC), the net animal weight gain or loss minus the weight of the tumor, was recorded as a function of beginning and ending weights. [Standard error of the mean and *P* values of probability that a difference in means between control and test groups was statistically significant (t test) were obtained but are not presented as part of this paper.] Synergy is defined as a combined antitumor effect (E_{ab}) which exceeds the sum of the individual antitumor effects ($E_a + E_b$), so that $E_{ab} > E_a + E_b$ (10). Animals were maintained on Agway Prolab rat chow and water ad libitum.

Methotrexate (Bristol Laboratories, Syracuse, NY) and vitamin K_3 (menadione sodium bisulfite, Sigma Chemical Co, St. Louis, MO) were put into buffered saline solution and used as such; solutions were prepared fresh daily for injection.

RESULTS

The in vivo response of Walker 256 im carcinosarcoma to vitamin K_3 and methotrexate, alone and in combination, is shown in table 1 (confirmed by multiple experi-

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TABLE 1.—Effect of combination of vitamin K_3 and methotrexate in Walker 256 carcinosarcoma in rats

Dose (mg/kg/day)		AWC (g)		% tumor inhibition		
Vitamin K_3	Methotrexate	Treated rats	Saline controls	Vitamin K_3	Methotrexate	Vitamin K_3 and methotrexate
100	0.15	15.7	7.4	18	77	67
100	0.125	15.5	7.4	18	59	61
100	0.10	12.5	7.4	18	43	34
100	0.075	7.4	7.4	18	12	17
200	0.15	5.6	7.4	30	77	95
200	0.125	5.1	7.4	30	59	87
200	0.10	4.0	7.4	30	43	86
200	0.075	6.6	7.4	30	12	78
250*	0.075	−7.6	7.1	39	21	99
225	0.075	0.3	7.1	37	21	84
200	0.075	5.0	7.1	24	21	75
175	0.075	3.7	7.1	25	21	42
150	0.075	6.1	7.1	26	21	37

*2 toxicity deaths.

ments). The upper part of this table demonstrates the usual dose-response tumor inhibition curve of methotrexate (percent tumor inhibition, methotrexate) as well as synergy (percent tumor inhibition, vitamin K_3 and methotrexate), most evident in the lower dosages of methotrexate, with vitamin K_3 at its higher test level. For example, the sum of tumor inhibition of methotrexate at a dose of 0.075 mg/kg/day (12%) and of vitamin K_3 at a dose of 200 mg/kg/day (30%) was 42%; their combined effect (vitamin K_3 and methotrexate) resulted in a tumor inhibition of 78%. On the other hand, no synergy could be demonstrated using vitamin K_3 at the lower dose level of 100 mg/kg/day.

The lower part of table 1 indicates the effect of varying the dose of vitamin K_3 while holding steady the dose of methotrexate at 0.075 mg/kg/day. Note that synergy appears at the higher dose levels of vitamin K_3 but disappears at levels of vitamin $K_3 < 200$ mg/kg/day. Both the upper and lower portions of table 1 thus indicate an apparent minimum "threshold" level of vitamin K_3 necessary for synergy.

Toxicity was not significant. It was manifested in weight loss at vitamin K_3 doses of 225 and 250 mg/kg/day (not shown) and in one animal death at 225 mg/kg/day (not shown); two deaths from toxic effects occurred with the combination dose of vitamin K_3 at 250 mg/kg/day. Excessive weight loss or animal deaths were not seen with vitamin K_3 below levels of 225 mg/kg/day, either alone or in combination.

DISCUSSION

Methotrexate is an antifolate chemotherapeutic agent active against a wide variety of rapidly proliferating neoplastic tissue and limited in clinical utility chiefly by its toxicity; this utility can be extended to some degree by the concurrent use of leucovorin as a rescue for methotrexate. However, previous in vitro data of Chlebowski et al (7,8), reinforced by the in vivo data of the present study, suggest a very definite synergy between the common naphthoquinone vitamin K_3 and methotrexate, even in low doses of methotrexate which (in the present study) show only meager in vivo antitumor effect per se and which, in combination with sufficient amounts of vitamin K_3 to produce synergy, elicit no apparent alterations in host response from control animals. Should this synergy between vitamin K_3 and methotrexate extend to human neoplasms, in consonance with in vitro and in vivo data thus far obtained, such a situation could significantly enhance the effectiveness and clinical applicability of methotrexate and sharply increase this agent's potential in the treatment of cancer.

The present study also suggests a minimum threshold dose of vitamin K_3 necessary for methotrexate synergy and beyond such a minimum, with ascending doses of vitamin K_3, a dose-response relationship. While it is not yet known what levels of vitamin K_3 are necessary to achieve such a minimum synergizing effect in man, preliminary data indicate that plasma levels of vitamin $K_3 \leq 1$ μM, similar to those associated with in vitro cytotoxicity (11) and presumably sufficient to induce synergy, can be achieved after only a single dose of menadiol sodium diphosphate (converted in vivo to menadione) of 20 mg/m^2 (12).

No increase in toxicity accompanied vitamin K_3 administration in doses at which synergy was still pronounced. This lack of toxicity has been correspondingly observed in ongoing clinical trials of menadiol sodium diphosphate (8) and in early phase I trials of vitamin K_3 administered at doses of 400–500 mg/day (about 50 times the normal dose) over 3–5 consecutive days (13). These data are in agreement with the clinical experience of > 40 years which has shown vitamin K_3 to be a safely tolerated agent in man.

CONCLUSION

Vitamin K_3 has been shown to be synergistic with methotrexate in in vitro as well as in the present in vivo studies. Such synergy, if extended to human neoplasms,

may significantly multiply the effectiveness of methotrexate as an antitumor agent as well as increase the spectrum of tumors susceptible to this drug's action.

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BRIEF REPORTS

Peak Cerebrospinal Fluid Platinum Levels in a Patient With Ependymoma: Evaluation of Two Different Methods of Cisplatin Administration[1,2]

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Peak CSF and serum platinum levels were examined in a patient with ependymoma after each of four consecutive cisplatin doses of 100 mg/m² administered by either 30-minute or 3-hour infusion. Both infusion lengths produced similar peak CSF platinum levels within 2 hours after the completion. Ultrafiltrate serum platinum levels correlated with the CSF platinum levels, whereas total plasma platinum did not. No differences in clinical toxicity or response were seen between the two methods of administration. Based on these preliminary results, similar peak CSF platinum concentrations are achieved by 30-minute or 3-hour infusions, and ultrafiltrate serum platinum concentrations can be used to predict these levels. [Cancer Treat Rep 70:1437-1438, 1986]

Cisplatin therapy has been shown to be an effective salvage therapy for patients with recurrent brain tumors (1). The CSF pharmacokinetics of cisplatin are difficult to perform in man, and the lack of such information makes it difficult to predict blood-brain barrier penetration of the cytotoxic fraction of cisplatin. Since the intact cisplatin complex is responsible for cytotoxicity and the majority of cisplatin is metabolized or eliminated within the first 4 hours after therapy (2), the peak cytotoxic CSF platinum levels are probably achieved within a short period after the end of a cisplatin infusion.

In the present study, we examined the CSF and serum platinum levels after alternating 30-minute and 3-hour infusions of 100-mg/m² doses of cisplatin in a patient with ependymoma.

PATIENTS AND METHODS

The patient was a 3-year-old boy with recurrent ependymoma who was initially treated with debulking surgery and radiation therapy. Previous chemotherapy included four doses of vincristine. Prior to the first admission for cisplatin therapy, he underwent further surgery for progressive disease at which time an Omaya reservoir was placed in the left ventricle.

The patient received a 100-mg/m² dose of cisplatin every 3 weeks by alternating 30-minute and 3-hour infusions, for a total cumulative dose of 400 mg/m². Blood and CSF samples were drawn before treatment, immediately following the infusion, and 30, 60, and 120 minutes after each dose. In all cases blood specimens were drawn approximately 3-5 minutes after each CSF sample. Platinum concentrations were quantified by atomic absorption spectrometry as previously described (3).

RESULTS

Figure 1 shows the peak total serum, serum ultrafiltrate, and CSF platinum concentrations. Both ultrafiltrate serum and CSF platinum concentrations accounted for a small percentage of the total serum platinum, which is consistent with previous reports (3-5). In agreement with our other case report, CSF platinum levels were similar to ultrafiltrate serum platinum levels (3). This would suggest that only small molecular weight platinum complexes are transported across the blood-brain barrier and that ultrafiltrate serum platinum concentrations can be used to predict CSF platinum levels. No difference between ultrafiltrate CSF and total CSF platinum concentrations was seen.

Both 30-minute infusions resulted in peak CSF levels

[1] Received Mar 31, 1986; revised July 22, 1986; accepted Aug 1, 1986.
[2] Supported in part by the Louis R. Lurie Foundation, the Northern California Cancer Program, and the Randy Lynn Baruh Research Foundation.
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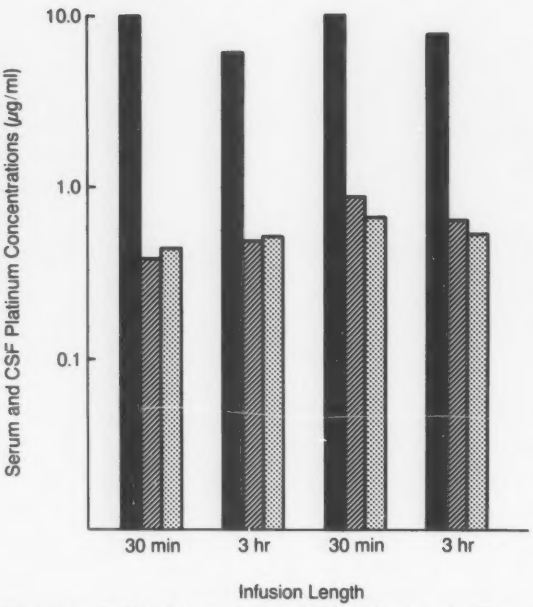

FIGURE 1.—Peak total serum platinum (solid bars), serum ultrafiltrate platinum (diagonal lines), and peak CSF platinum (dots) after each 100-mg/m^2 dose. Each concentration is the average of at least 3 platinum determinations.

between 1 and 2 hours after the infusions, whereas the 3-hour infusions resulted in peak CSF platinum between the end of the infusions and 30 minutes after the infusions. Peak CSF platinum levels were similar with both infusions. Values for area under the curve for the CSF versus time (0–2 hours) for the 30-minute and 3-hour infusions were 52.2 and 48.0 μg/ml/minute, respectively.

DISCUSSION

The successful treatment of refractory brain tumors with iv cisplatin therapy suggests that the active fraction of cisplatin is transported across the blood-brain barrier. Many investigators believe that the active portion of cisplatin remains unbound to plasma proteins (ultrafiltrate) and is rapidly eliminated or metabolized to an inactive platinum complex (2). Therefore, the most clinically relevant CSF platinum levels would be achieved within a short period after either a bolus dose or short infusion. In the present study, we show that ultrafiltrate serum platinum levels correlate with CSF platinum concentrations, and that 30-minute and 3-hour infusions produced similar peak CSF platinum concentrations.

Recently, we reported a reduction of cisplatin-induced neurotoxicity in patients receiving a modified dosing schedule of high-dose cisplatin therapy (100 mg/m^2 on Days 1 and 8 by a 3-hour infusion) (6). We showed that the accumulation of ultrafiltrate plasma platinum complexes does not occur with our dosing regimen, whereas it did occur with the traditional 5-day regimens (40 mg/m^2/day for 5 days by a 1-hour or 30-minute infusion) (7,8). These differences in the pharmacokinetics of ultrafiltrate plasma platinum may be one explanation for the reduction of neurotoxicity seen in the previous study. Since we show no differences in either peak CSF levels or CSF areas under the curves using either 30-minute or 3-hour infusions, this would support our hypothesis that the reduction of cisplatin neurotoxicity, if centrally mediated, may be related to the dosing intervals rather than rate of infusion.

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Idarubicin in Advanced Breast Cancer: A Phase II Study[1]

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Twenty-nine patients with metastatic breast cancer were treated orally with idarubicin (15 mg/m^2 × 3 days every 3–4 weeks). Objective response was seen in 31% of all patients. Toxicity was acceptable. There should be further clinical trials of the new anthracycline antibiotic. [Cancer Treat Rep 70:1439–1440, 1986]

Idarubicin (4-dmDNR) is a new anthracycline which entered clinical trials because it showed high potency in vitro in preclinical studies, favorable therapeutic index, particularly reduced relative cardiotoxicity in animal studies (1), and therapeutic activity on iv and oral administration (2). Pharmacokinetic evaluation of 4-dmDNR by iv and oral administration in mice revealed that the parent drug was metabolized extensively to 4-demethoxy-daunorubicinol. This was the only metabolite; it was retained for prolonged periods and itself had antitumor activity (3). Phase I studies of 4-dmDNR indicated that the dose of 40–50 mg/m^2 orally every 3–4 weeks could be safely given to patients (4). In our institute, a phase II study has been conducted to assess antitumor activity and toxicity of 4-dmDNR given orally to patients with advanced breast cancer.

PATIENTS AND METHODS

Twenty-nine patients with histologically proven breast cancer were entered in this study (table 1). Patients were eligible according to the following criteria: presence of bidimensionally measurable metastases or lytic bone lesions; previous treatment-free interval ≥ 4 weeks and no previous exposure to anthracyclines; ≤ 65 years of age; performance status < 3 [Eastern Cooperative Oncology Group (ECOG) scale]; normal hemogram, serum chemistry, and at-rest values of left ventricular ejection fraction (LVEF ≥ 50% with radionuclide angiography); and informed verbal consent.

4-dmDNR was supplied by Farmitalia Carlo Erba, Milan, Italy; it was administered every 3 weeks orally as a gelatine capsule at a dose of 15 mg/m^2 × 3 days. To avoid the risk of cardiotoxicity, we planned to stop the treatment at a total dose of 450 mg/m^2 if no disease progression or unacceptable toxicity was observed.

If hematologic recovery (wbc count ≥ 3500/mm^3; platelet count ≥ 100,000/mm^3; and hemoglobin ≥ 12 g/100 ml) had not occurred in 3 weeks, the treatment was delayed by 1 week. Physical examination, serum chemistries, blood cell counts, and ECG were performed for each course. Patients had chest x-rays and cardiac examination, with evaluation of LVEF every three to four courses.

Other investigations (x-rays, radioisotopic scan, and echography) were performed when necessary to assess the response to treatment. Patients were evaluated for response and toxicity according to World Health Organization criteria (5). Complete response (CR) was defined as the disappearance of all lesions for at least 4 weeks; partial response (PR) was defined as a ≥ 50% decrease in the sum of the products of the two largest perpendicular diameters for bidimensional lesions and a decrease in size and recalcification of lytic bone metastases for at least 4 weeks.

RESULTS

All patients were evaluable for response and toxicity. There were two early deaths. One patient with liver metastases experienced intolerable gastrointestinal toxicity (nausea and vomiting, grade 3; diarrhea, grade 3;

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total entered	29
Median age in yrs (range): 60 (48–65)	
Median performance status (range)*: 0 (0–2)	
Menopausal status	
Premenopausal	3
Postmenopausal	26
Dominant site of metastases	
Viscera	11
Bone	11
Soft tissue	7
Previous treatment	
Adjuvant setting	
Hormone therapy	6
Chemotherapy	14
Radiotherapy	5
Metastases	
Hormone therapy	17
Chemotherapy	7
Radiotherapy	10

*ECOG scale.

and mucositis, grade 1), required hospitalization for drug-related neutropenia and fever, and refused further therapy. Patients received a median number of three courses of therapy (range, one to 12 courses). Two patients received 12 courses because they did not show signs of cardiotoxicity and were still responding to the treatment.

The median total dose administered to each patient was 135 mg/m^2 (range, 45–540). The results of the study are as follows: nine of 29 objective responses (31%) [one CR (3%) and eight PRs (28%); 95% confidence limits, 15%–51%]. Ten of 29 patients (34%) had disease progression. All objective responses were observed in patients pretreated with chemotherapy (cyclophosphamide, 600 mg/m^2; methotrexate, 40 mg/m^2; and 5-fluorouracil, 600 mg/m^2 on Day 1 every 21 days iv) in the adjuvant setting and for all dominant sites of metastases; the CR was observed in a patient with lung metastases. Patients who had failed to respond to first-line chemotherapy for metastases also failed to respond to this new agent.

Median survival from the beginning of the treatment was 6 months (range, 1–18.5+). Median duration of objective response was 6 months (range, 3–16+). Toxicity observed was as follows: nausea and vomiting occurred in 59% of the patients (grade 1, 30%; grade 2, 18%; and grade 3, 11%); partial alopecia occurred in 41% of the patients (grade 1, 22%; and grade 2, 19%); and leukopenia evaluated on Day 21 was observed in 37% of the patients (grade 1, 8%; grade 2, 22%; and grade 3, 7%). The treatment for these patients was delayed by 1 week. Diarrhea was recorded in 15% of the patients, stomatitis in 11%, anemia in 7%, and fever in 7%.

Until now, we have observed only two decreases > 10% of LVEF: 11% and 19% reduction in two patients who received 135 and 450 mg/m^2 of 4-dmDNR, respectively, but with final values of LVEF > 50%. We did not observe clinical signs of cardiotoxicity.

CONCLUSIONS

4-dmDNR is a new anthracycline active in advanced breast cancer. The response rate of 31% is comparable to that observed with other anthracyclines used as single agents. Systemic toxicity observed was similar in nature but less severe than with the parent compound at equimyelotoxic doses. If one also considers the risk of local necrosis following accidental extravasation, which may occur with doxorubicin or daunorubicin, then the use of an oral analog has obvious advantages, provided it proves to be equieffective in larger trials.

Until now, no sign of cardiotoxicity has been observed, but for a definitive evaluation longer times of observation and higher total administered doses are needed. Martoni et al (6) reported comparable results with our trial in a phase II study in pretreated breast cancer patients.

This new drug, which exerts good antitumor activity by the oral route and is generally well-tolerated, is of great interest for clinical trials, particularly in the long-term outpatient setting.

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BRIEF REPORTS

Cytarabine and Cisplatin in Advanced Malignant Melanoma[1]

Emilio Bajetta,* Claudio Verusio, Valeria Bonfante, and Gianni Bonadonna[2]

Twenty-seven consecutive patients with advanced malignant melanoma were treated with cytarabine (Ara-C) and cisplatin. Of 25 evaluable patients, four achieved partial response, for a median duration of 3 months. Three of four responders belonged to the group of seven patients given Ara-C at a dose of 3 g/m^2. The predominant toxic effect was hematologic and related to the dose of Ara-C. The cost-benefit ratio of this combination is inferior to that of dacarbazine or carmustine alone. [Cancer Treat Rep 70:1441-1442, 1986]

Both cytarabine (Ara-C) and cisplatin (CDDP) are moderately effective as single agents in metastatic malignant melanoma (1,2). Their proposed in vitro synergism (3,4) has recently stimulated phase I clinical trials. Favorable responses have been reported in patients with non-Hodgkin's lymphomas, but these remissions have generally been brief (5). In other neoplastic diseases results were poor (6-8). However, the above-mentioned trials were performed in far-advanced malignancies refractory to other agents and may not accurately reflect the actual potential utility of the combination. The aim of our study was to test antitumor activity and toxicity of Ara-C plus CDDP in advanced malignant melanoma with minimal prior chemotherapy.

PATIENTS AND METHODS

From December 1984 to August 1985, 27 consecutive patients with metastatic malignant melanoma were entered in the study.

Patients were required to have histologically confirmed diagnosis and measurable disease, age < 70 years, Karnofsky performance status ≥ 60, life expectancy > 1 month, adequate bone marrow reserve, blood chemistry within normal limits, and no prior therapy with Ara-C or CDDP. Eleven patients presented with metastatic disease localized to one anatomic site, nine had two sites involved, and five had multiple metastatic involvement. Seven patients presented with soft tissue involvement only and 18 presented with visceral disease, 14 of them with lung metastases. Asymptomatic brain metastases were documented in four patients; in only one patient was the brain the only site of metastatic disease. Six patients (24%) were previously treated with chemotherapy (dacarbazine, three patients; other drugs, three). The planned treatment regimen consisted of the concurrent administration of both drugs on Days 1 and 2. Ara-C (3 g/m^2/day) was given by 3-hour iv infusion in 1000 ml of 0.9% saline solution and CDDP (40 mg/m^2/day) was given by 3-hour iv infusion in 500 ml of 5% dextrose solution. Chemotherapy was then followed by 1000 ml of 5% dextrose solution with 20 mEq/L of KCl. Patients were advised to drink at least 1 L of fluid during the day preceding and the day following treatment. In the presence of complete bone marrow recovery, cycles were repeated every 3 weeks. In the absence of progressive disease, a minimum of two treatment cycles were required to define drug response. In patients showing stable disease or objective tumor response, chemotherapy was continued for a maximum of six treatment cycles. Before each treatment cycle, physical examination with tumor measurement, hemogram, and blood chemistry was repeated, as well as x-rays and scans if indicated by the clinical situation. During therapy, cbcs with differential and platelet counts were performed weekly.

Complete response was defined as the complete disappearance of all tumor lesions for at least 1 month. Partial response (PR) was defined as a $> 50\%$ decrease in the product of the two largest perpendicular diameters of all measurable lesions for a minimum of 1 month.

RESULTS

Twenty-five of 27 patients were evaluable for toxicity and therapeutic activity. Of the two nonevaluable pa-

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TABLE 1.—Toxic effects in 25 evaluable patients*

Toxic effect	No. of Ara-C doses (g/m^2/day) 3 ($n = 7$)	2 ($n = 5$)	1.5 ($n = 13$)	Total (%)
Nausea and vomiting	7	5	13	25 (100)
Alopecia	2	1	2	5 (20)
Skin rash	1	—	1	2
Anemia (Hgb fall > 4 g/100 ml)	4	1	5	10 (40)
Leukocyte count < $1000/mm^3$	1	1	0	2
Platelet count < $50,000/mm^3$	4	2	2	8 (32)
Infection and fever	3	1	3	7 (28)
Nephrotoxicity	0	1	1	2
Diarrhea	3	1	2	6 (24)

*n = No. of patients.

tients, one had received less than one full cycle of therapy because of skin rash interpreted as allergic reaction, and the other was lost to follow-up after the first treatment cycle. Among evaluable patients, four received only one cycle and seven received two cycles because of rapid disease progression. Only 21 cycles were given with the initial planned dose (3 g/m^2/day) of Ara-C. The dose was reduced to 2 g/m^2/day in five patients and then to 1.5 g/m^2/day in 13 patients because of severe bone marrow suppression (in particular, thrombocytopenia). No patient achieved complete response. PR was achieved in four of 25 (16%) evaluable patients and only in untreated patients. Three of the four responses occurred in females and in patients given Ara-C at a dose of 3 g/m^2/day. Tumor shrinkage was observed in patients with disease confined to lymph nodes or lungs. In all patients PR was documented during the first three treatment cycles. The median duration of PR was 3 months (range, 2–5), and median overall survival was 5.5 months.

Toxic effects are shown in table 1. No treatment-related deaths were observed. Myelosuppression was the dose-limiting toxic effect. Leukocyte and platelet count nadirs occurred from Day 10 to Day 14. Prolonged myelosuppression caused treatment delay for 1 week in eight of 67 cycles administered. We observed fever and infection in seven patients, three of whom were treated with 3 g/m^2/day, but none of the episodes was life-threatening. Of the seven patients given Ara-C at 3 g/m^2/day, severe thrombocytopenia occurred in four, and in the only patient previously treated with dacarbazine the platelet count nadir was $17,000/mm^3$. There were no episodes of bleeding and in all instances the platelet count returned within normal limits by Day 21. Two episodes of skin rash were observed and in both instances treatment was discontinued. A transient increase in serum creatinine (1.7 and 1.65 mg/100 ml) was documented in two patients. Moderate to severe asthenia occurred in most patients.

CONCLUSION

The results of our prospective study indicate that Ara-C plus CDDP has only marginal activity in advanced malignant melanoma, even if most patients were previously untreated with chemotherapy. However, it cannot be excluded that the regimen might have higher antitumor activity than observed if the highest doses were consistently applied with aggressive supportive therapy. Our clinical findings are in line with those of Howell and Gill (9), who have recently reported lack of significant synergistic interaction in vitro between Ara-C and CDDP. Thus, for the time being, either dacarbazine or carmustine remains the drug of first choice in the treatment of metastatic malignant melanoma.

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Effect of Cimetidine and Ranitidine on the Metabolism and Toxicity of Hexamethylmelamine[1,2]

Kenneth Hande,* Gregory Combs, Roger Swingle, G. Louis Combs, and Lowell Anthony[3]

In a rat model, doses of 20–120 mg/kg of cimetidine prolonged in a dose-related manner the half-life of hexamethylmelamine by 29%–80%, while doses of 1–25 mg/kg of ranitidine did not. Administration of 120 mg/kg of cimetidine with a single 350-mg/kg dose of hexamethylmelamine increased toxicity from LD30 to LD75 ($P = 0.005$). When combined with 25 mg/kg of ranitidine, a statistically insignificant ($P = 0.16$) 15% increase in hexamethylmelamine toxicity was noted. These studies indicate that cimetidine but not ranitidine increases the toxicity of hexamethylmelamine through inhibition of microsomal metabolism. [Cancer Treat Rep 70:1443–1445, 1986]

Cimetidine and ranitidine are histamine H_2 antagonists used for the treatment of diseases caused by gastric hyperacidity. Evidence has accumulated that cimetidine can alter drug metabolism through its ability to inhibit the hepatic microsomal cytochrome P_{450} enzyme system (1). Ranitidine binds less avidly to microsomal enzymes and, in clinical dosage, does not appear to significantly alter microsomal metabolism (2). Ranitidine is four- to five-fold more potent an H_2-antagonist than cimetidine, and its dosage is proportionately lower. Several antineoplastic drugs, including cyclophosphamide, the nitrosoureas, doxorubicin, procarbazine, and hexamethylmelamine, undergo metabolism via the hepatic oxidative microsomal enzyme system. We have evaluated the effect of cimetidine and ranitidine on the metabolism and toxicity of antineoplastic agents using hexamethylmelamine as a model drug since: (*a*) essentially all metabolism and clearance of this agent occur via hepatic microsomal N-demethylation, and (*b*) radiolabeled compound is available which allows for a simple, rapid determination of drug half-life in vivo (3). To test our model system, aminopyrine breath tests, which have previously been used for analysis of microsomal function (4,5), have also been performed.

MATERIALS AND METHODS

^{14}C-Aminopyrine (80 mCi/mmol) was purchased from New England Nuclear Corp, Boston, MA. ^{14}C-Hexamethylmelamine, labeled on the six methyl groups (5.78 mCi/mmol), was supplied by Dr. Robert Engel, National Cancer Institute, Bethesda, MD. One hour after receiving either saline, cimetidine, or ranitidine, male Sprague-Dawley rats (150–250 g) were given 0.5 μCi of ^{14}C-aminopyrine or ^{14}C-hexamethylmelamine in a volume of 0.5 ml of saline via ip injection. Rats were housed in individual airtight restraining cages. Exhaled $^{14}CO_2$ was trapped in 10 ml of 2:1 (vol/vol) methanol:ethanolamine and counted. Exhaled $^{14}CO_2$, as measured by the total counts per minute per collection period, peaked and then decreased monoexponentially over the monitored time period. The elimination rate constant (Kel) was calculated by a least-square regression analysis of the logarithm of the amount of $^{14}CO_2$ produced with respect to time after peak. The elimination half-life was calculated by dividing 0.693 by the elimination rate constant. Each treatment half-life was compared to a control half-life determined in the same animal under identical conditions within 72 hours of the treatment study. Statistical

[1] Received Apr 16, 1986; revised Aug 5, 1986; accepted Aug 13, 1986.
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comparisons were made by two-tailed paired Student's t-test.

RESULTS

As noted in previous studies (4), treatment of rats with doses of 20–120 mg/kg of cimetidine produced a lower peak $^{14}CO_2$ excretion rate, a delay in time to peak $^{14}CO_2$ excretion, and progressive prolongation in aminopyrine half-life. At doses of 1–25 mg/kg of ranitidine (ie, doses which produce H_2 receptor inhibition comparable to 5–120 mg/kg of cimetidine), only a slight and variable increase in aminopyrine half-life was found (table 1). Treatment of rats with cimetidine produced a lower peak $^{14}CO_2$ excretion rate, a delay in time to peak $^{14}CO_2$ excretion, and a prolongation of $^{14}CO_2$ excretion following administration of ^{14}C-hexamethylmelamine (table 1). Administration of 1 and 25 mg/kg of ranitidine produced only slight (15%) and non-statistically significant prolongation in hexamethylmelamine half-life.

The effect of cimetidine and ranitidine administration on the toxicity of hexamethylmelamine was determined using age-matched, male Sprague-Dawley rats (50–100 g). Three groups of 20 rats were given 350 mg/kg of hexamethylmelamine 1 hour after ip administration of 0.1 ml of either: (*a*) saline, (*b*) 120 mg/kg of cimetidine, or (*c*) 25 mg/kg of ranitidine. All rats were given six additional doses of saline, cimetidine, or ranitidine every 12 hours and followed until death. Administration of cimetidine with hexamethylmelamine killed 75% of animals compared with 30% of controls ($P = 0.005$). Administration of ranitidine with hexamethylmelamine killed 45% of animals ($P = 0.04$ vs cimetidine treatment). The increase in toxicity of ranitidine-treated animals over controls was not statistically significant ($P = 0.16$).

DISCUSSION

Cimetidine inhibits the microsomal metabolism of a number of drugs in man, whereas ranitidine, at usual therapeutic dosage, does not (1,2). The present studies have extended these observations to the antineoplastic drug hexamethylmelamine using breath tests in an animal model. Doses of cimetidine and ranitidine used in these experiments are comparable, since ranitidine is a four- to five-fold more potent H_2-antagonist than cimetidine. The doses of cimetidine and ranitidine used in rats are high on a per kilogram basis when directly related to man. However, when compared on a body surface area basis (6), the highest dose of cimetidine is 114% and that of ranitidine is 140% of those recommended for use in man.

H_2-receptor antagonists are commonly used to treat gastrointestinal symptoms occurring in patients receiving cancer chemotherapy. Little information is available regarding the effect of H_2-antagonists on antineoplastic drug metabolism. Although it remains an investigational agent, hexamethylmelamine has activity against several human tumors, including small cell lung cancer and ovarian cancer (7). Essentially all metabolism and clearance of this agent occur via microsomal *N*-demethylation. The active metabolite of hexamethylmelamine remains uncertain. Ames et al (8) have shown that as hexamethylmelamine is metabolized via the cytochrome P_{450} system, an active intermediate (*N*-methylolpentamethylmelamine) is formed which acts as a DNA alkylating agent. Our studies suggest that inhibition of the microsomal enzyme system resulting in slower and more prolonged formation of this metabolite increases toxicity. The metabolic activation of hexamethylmelamine is similar to that of other antitumor agents, including cyclophosphamide, nitrosoureas, and procarbazine. It is likely that a similar increase in toxicity of these agents will result from slower, more prolonged formation of active metabolites. Dorr et al (9) have shown that the concomitant administration of cimetidine produced a delayed time to peak concentration of active cyclophosphamide metabolites as well as a slower clearance rate of total metabolites. Two reports (10,11) have suggested an increase in toxic side effects when nitrosoureas have been given with cimetidine, but the mechanism for such increased toxicity has been unexplained. Pending further clinical studies, we suggest that H_2-antagonists not be given in combination with microsomally metabolized antineoplastic drugs unless clearly indicated, and that in such situations ranitidine be the H_2 antagonist of choice.

TABLE 1.—Effect of histamine H_2-antagonists on aminopyrine and hexamethylmelamine half-life

Treatment (mg/kg)	Average increase in aminopyrine half-life ± SD	Increase in hexamethylmelamine half-life ± SD
Cimetidine		
5	17% ± 15% ($P = 0.13$)	10% ± 27% ($P = 0.79$)
20	50% ± 24% ($P < 0.01$)	29% ± 30% ($P = 0.04$)
40	91% ± 28% ($P < 0.01$)	54% ± 21% ($P < 0.01$)
80	150% ± 81% ($P < 0.01$)	67% ± 55% ($P = 0.01$)
120	275% ± 216% ($P < 0.01$)	80% ± 40% ($P < 0.01$)
Ranitidine		
1	9% ± 17% ($P = 0.23$)	9% ± 43% ($P = 0.74$)
10	16% ± 14% ($P = 0.01$)	—
25	5% ± 18% ($P < 0.56$)	—
60	2% ± 13% ($P < 0.58$)	—
120	33% ± 13% ($P < 0.01$)	11% ± 34% ($P = 0.25$)

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BRIEF REPORTS

Phase II Trial of Mitomycin, Vindesine, and Hexamethylmelamine in Metastatic Non-Small Cell Bronchogenic Carcinoma[1,2]

Philip D. Bonomi,[3,*] Richard Pazdur,[3] Leo Stolbach,[4] Bernard Mason,[5] and David Ettinger[6]

Mitomycin (10 mg/m² iv on Day 1), vindesine (3 mg/m² iv on Days 1 and 8), and hexamethylmelamine (100 mg/m²/day orally on Days 1–14) was administered to 32 patients with metastatic non-small cell bronchogenic carcinoma. No patient had been previously treated with chemotherapy and Eastern Cooperative Oncology Group (ECOG) performance status was 0–1 in 21 of 32 patients. Eleven partial responses (34%) were observed, with a median duration of 9 weeks. No complete responses were observed in this group of patients, whose median survival duration was 22 weeks. Moderate leukopenia (median leukocyte count nadir, 2500/mm³) was the major toxic effect. Although this regimen is active and relatively nontoxic, it will not be utilized in future ECOG trials because it has not produced an apparent improvement in survival duration. [Cancer Treat Rep 70:1447–1448, 1986]

Approximately one-third of the patients with non-small cell bronchogenic carcinoma (NSCBC) present with metastatic disease. Although both single agents and combination regimens have produced objective tumor regressions in this group of patients, there is no conclusive evidence that chemotherapy has produced survival benefit (1). In an attempt to develop an active regimen for patients with stage III_{M1} NSCBC, mitomycin (2) and hexamethylmelamine (3) were combined because both had shown activity in phase II trials and because their dose-limiting toxic effects and mechanisms of action were different. This regimen produced an 18% response rate, with three responses occurring in patients who had received previous chemotherapy (4). Vindesine was added to this two-drug regimen because of the vinca alkaloid's activity in NSCBC (5) and because its platelet-stimulating effect (6) might offset thrombocytopenia, which is associated with mitomycin.

MATERIALS AND METHODS

Patients who had histologically confirmed stage III_{M1} NSCBC were eligible for this phase II trial. Other eligibility requirements included Eastern Cooperative Oncology Group (ECOG) performance status < 3, age < 70 years, no previous chemotherapy, leukocyte count $> 4000/mm^3$, platelet count $> 100{,}000/mm^3$, BUN < 25 mg/dl, serum creatinine < 1.5 mg/dl, bilirubin < 1.5 mg/dl, measurable or evaluable disease, and informed consent.

The treatment regimen was as follows: mitomycin (10 mg/m² iv) on Day 1, vindesine (3 mg/m² iv) on Days 1 and 8, hexamethylmelamine (100 mg/m²/day orally) in three to four divided doses on Days 1–14, and pyridoxine (100 mg orally) three times daily. Cbc and platelet counts were done weekly. Treatment was repeated every 21 days if toxicity permitted and all drugs were modified for hematologic toxicity. Doses of vindesine and hexamethylmelamine were modified for neurotoxicity.

Tumor measurements were done every 3 weeks, and responses were defined by previously described ECOG criteria (7).

RESULTS

All 32 patients who were entered in this protocol are evaluable for response, toxicity, and survival. Patient

[1] Received Apr 21, 1986; revised Aug 6, 1986; accepted Aug 19, 1986.

[2] This study was conducted by the Eastern Cooperative Oncology Group (*Paul P. Carbone, chairman*, CA-21115) and was supported by Public Health Service grants (CA) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Total	32
Median age in yrs (range): 57 (31–70)	
Sex	
Males	23
Females	9
Performance status	
0–1	21
2–3	11
Histology	
Adenocarcinoma	13
Squamous cell carcinoma	12
Large cell carcinoma	3
Undifferentiated non-small cell carcinoma	4
Previous weight loss	
0%–5%	15
> 5%	17
Previous thoracic radiation therapy	
Yes	12
No	20

characteristics are shown in table 1. The number of treatment cycles ranged from one to 12, with a median of three. The response rate was 34%, with all 11 responses being partial and all occurring in pulmonary or soft tissue lesions. The median duration of response was 9 weeks, and the median survival duration for the entire group was 22 weeks. The 1- and 2-year survival rates were 9% and 0%, respectively.

The median leukocyte count nadir was 2500/mm^3, with a leukocyte count < 1000/mm^3 observed in two patients, one of whom had a febrile episode from which he recovered. The lowest platelet count was 40,000/mm^3 and the median platelet count nadir was 156,000/mm^3.

Mild to moderate nausea and vomiting were reported in 52% of the patients. Seven patients were reported to have neurological toxicity, which included five with paresthesias involving distal extremities, one with mild weakness, and one with severe bilateral leg pain which disappeared following cessation of treatment. Four patients experienced increased dyspnea and dry cough without evidence of infection. Bilateral interstitial infiltrates were observed on chest radiographs in these patients and one of them had a pulmonary biopsy which showed fibrosis. Mitomycin was discontinued, and respiratory symptoms improved.

DISCUSSION

The response rate observed with mitomycin, vindesine, and hexamethylmelamine (MVH) is virtually identical to the 36% response rate reported for a trial of mitomycin combined with vindesine (8). During the first 6 weeks of treatment, the doses of mitomycin in the two-drug regimen (8) and in our regimen were identical, while our dose of vindesine was 20% less than the dose of vindesine in the two-drug regimen. The similarity of the doses of mitomycin and vindesine and of the response rates suggests that hexamethylmelamine probably added little to the activity of the MVH regimen.

Similar to the experience of Kris et al (8) with the mitomycin and vindesine regimen, the toxicity associated with MVH was not severe and this treatment could be given routinely on an outpatient basis. Conversely, the toxicity associated with MVH seems less than the toxicity observed with cisplatin regimens in a recently conducted ECOG study (9). There were no instances of fatal toxicity in MVH-treated patients compared to 5%–6% fatal toxic episodes in patients treated with the cisplatin-containing regimens (9).

Although the response rate and toxicity compare favorably with results observed in recent ECOG trials on NSCBC, the median survival duration of MVH-treated patients (22 weeks) does not appear better than the median survival durations (19–26 weeks) observed with other regimens (9). Therefore, MVH will not be included in future ECOG NSCBC studies, the objectives of which will be the identification of new active single agents and the development of new combination regimens which might have an impact on survival.

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BRIEF REPORTS

Central Nervous System Toxicity With Fludarabine[1,2]

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A serious delayed neurotoxicity marked by encephalopathy and cortical blindness has occurred in patients treated with fludarabine. This toxicity had only been reported in patients receiving high doses (ie, aplasia-inducing). We describe a similar subacute neurological deterioration occurring in two patients, including one who received only low doses of this agent. Neurologic vulnerability to low doses of fludarabine may be multifactorial and at present cannot be predicted. Continued caution in the use of this new antineoplastic agent is appropriate. [Cancer Treat Rep 70:1449–1450, 1986]

Fludarabine, a derivative of vidarabine, is a new anticancer agent currently undergoing phase I and II testing (1). Early phase II studies indicate that activity is seen in patients with acute myelogenous leukemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma including mycosis fungoides. At high doses (100–175 mg/m^2 × 5–7 days), serious delayed neurotoxicity has occurred (2). This toxicity became evident 3–10 weeks after treatment and consisted of blurred vision, diplopia, dysarthria, paresthesias, and weakness progressing to bilateral cortical blindness, confusion, and coma. Neurotoxicity in phase I trials has been dose-related, with no CNS toxicity reported at < 100 mg/m^2 × 5 days. We wish to report two additional cases of suspected fludarabine-associated delayed neurotoxicity occurring at significantly lower doses.

CASE REPORTS

Patient 1

Patient 1 was a 34-year-old woman with T-cell lymphoblastic leukemia who had previously achieved complete remission after two courses of cytarabine, 6-thioguanine, vincristine, doxorubicin, and prednisone. She was given a third course as consolidation and received eight doses of intrathecal methotrexate (10–12 mg) and 2400 rads of prophylactic cranial irradiation. After 11 months she relapsed and failed to achieve complete remission after two additional courses of the same agents. Lumbar puncture was normal except for the finding of rare "abnormal lymphocytes." She was treated with a single course of fludarabine (77 mg/m^2 × 5 days), perhaps achieving aplasia but not a remission. She was next treated with teniposide and ifosfamide, but remained in relapse. Two months after receiving fludarabine she became agitated and diaphoretic and developed myoclonic jerks while remaining responsive. There was bilateral horizontal nystagmus, occasional dysconjugate gaze, bilateral hyperreflexia, and upgoing plantar responses. Lumbar puncture revealed normal glucose; protein, 45 mg/dl (normal, 15–45); wbc count < 5 (all lymphocytes); rbc count, 12; and negative cultures. The next day she developed dysarthria and a generalized increase in muscle tone. Phenytoin was begun for periodic seizure-like activity. Electroencephalogram was diffusely abnormal and computerized tomographic (CT) scan of the brain with infusion of contrast was normal. Within 3 days she was comatose and had roving eye movements, which progressed to doll's eyes, rigid extremities, and generalized seizures. She died while still comatose 2 weeks after onset of neurologic symptoms. A postmortem examination was refused.

Patient 2

Patient 2 was a 66-year-old male who had mycosis fungoides for 7 years prior to receiving three courses of fludarabine, the first course at 18 mg/m^2/day × 5 days and the second two at 22.5 mg/m^2/day × 5 days. Past

[1] Received Feb 12, 1986; revised July 28, 1986; accepted Aug 20, 1986.
[2] Supported in part by Public Health Service grants CA-09434 and CA-22433 and contract N01-CM-57737 (Division of Cancer Treatment) from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by the American Cancer Society Texas Division Fellowship Program.
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history was remarkable for mumps encephalitis at age 13 with complete recovery. Seventy-seven days after his first dose of fludarabine and 19 days after his last dose, he had lightheadedness, confusion, and weakness. Neurological examination was normal, and CT scan with infusion showed a possible old left basal ganglion infarct and moderate cerebellar atrophy. Lumbar puncture was normal, and protein level was 15 mg/dl. CSF cultures and India ink stain were negative. Serum B12 was slightly low at 187 pg/ml (normal, 210–920). Over the next month he noted worsening memory, increasing confusion, and stumbling. Examination at this time revealed a new right ptosis with right facial nerve paresis and a left-beating rotary nystagmus. Motor strength was normal but tone was slightly increased; gait was wide-based. Tendon reflexes, depressed 1 month previously, were now increased diffusely and plantar reflexes were down-going. A repeat lumbar puncture showed a slightly elevated protein level of 52 mg/dl, normal glucose, normal levels of myelin basic protein, and a few "atypical degenerating cells." Electroencephalogram and audio- and visual-evoked responses were normal. Serum B12 level was again slightly depressed at 197 pg/ml, and though a Schilling's test was normal he was empirically treated with parenteral B12. One week later he had a complete right Bell's palsy and was placed on prednisone (60 mg/day). After 1 month his Bell's palsy resolved, but he reported several episodes of transient blindness and he seemed more confused. Plantar reflexes were now upgoing, and gait was wide-based and ataxic. He had a marked decrease in visual acuity consistent with cortical visual loss, and later bilateral optic atrophy was evident. CSF was acellular with protein again slightly elevated at 51 mg/dl. Repeat CT scan was unchanged. Evoked responses were again normal, and magnetic resonance imaging demonstrated only mild periventricular abnormalities but no focal areas of demyelination. Electroencephalogram now showed a diffuse slow-wave abnormality.

Neurologic deterioration continued, with stupor progressing to coma. The patient died 200 days after receiving his first dose of fludarabine. Autopsy was remarkable for subacute demyelination of the optic nerves, with myelin breakdown products seen in macrophages and sparse surrounding gliosis. Bodian stain showed fair axonal preservation, which was confirmed by electron microscopy. The cerebral peduncles at the level of the midbrain and the white matter of the basis pontis had recent spongiotic demyelination, without glitter cells or gliosis. There was perivascular infiltration by mycosis fungoides cells at the cerebellopontine angle with (probably) secondary demyelination of CN VII. Hematoxylin and eosin and Luxol-fast-blue stains of cerebral and cerebellar white matter were normal.

DISCUSSION

We believe that our patients are similar to those previously reported in that the onset of neurologic symptoms was delayed and included spasticity, seizures, encephalopathy, and in one patient, blindness. The second patient is particularly troubling in that neurotoxicity has not been previously associated with this low dose of fludarabine. His clinical and autopsy findings cannot be attributed solely to leptomeningeal mycosis fungoides (3).

The neurotoxicity seen with fludarabine may be a leukoencephalopathic or myelinoclastic disorder, and seems to have a predilection for the optic fibers. Postmortem examination in one case of high-dose fludarabine neurotoxicity demonstrated multiple areas of leukoencephalopathy involving the subcortical white matter, optic nerves, chiasm, and tract (4). In our patient there was also demyelination of the optic nerves, as well as of the cerebral peduncles and pons. The pontine lesions were similar to those described in other patients who had received methotrexate and cranial irradiation (5) and do not seem specific to fludarabine.

These two patients may have been unusually sensitive to fludarabine for several reasons. A delayed necrotizing encephalopathy with confusion, ataxia, and stupor has been associated with intrathecal methotrexate, especially in combination with cranial irradiation, and may be exacerbated by subsequent treatment with cytarabine (6). Perhaps a similar mechanism was operative in our first patient. The second patient may have been more vulnerable to fludarabine neurotoxicity because of his marginally low B12 level or meningeal mycosis fungoides. The pharmacokinetics of fludarabine might have been altered in these two patients, resulting in unusually high levels of a toxic metabolite.

None of the other 222 patients treated with similar doses (median, two treatment cycles) of fludarabine on various Southwest Oncology Group phase II protocols have developed this clinical syndrome. Low-dose fludarabine may only infrequently cause severe leukoencephalopathy and optic neuropathy. Nonetheless, caution in the use of this promising new antineoplastic agent is warranted.

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BRIEF REPORTS

Antagonism of 5-Aza-2′-deoxycytidine Antileukemic Activity by Concomitant Treatment With Cytarabine[1,2]

Tina Colombo, Cosmo Rossi, and Maurizio D'Incalci[3,*]

In this study we show that cytarabine given simultaneously with 5-aza-2′-deoxycytidine (Aza-dC) antagonized Aza-dC activity against L1210 mouse leukemia. This antagonism was seen after a single dose (on Day 3 or Day 5 after tumor implant) and after repeated doses. This observation suggests caution in combining cytarabine with Aza-dC in the treatment of human leukemias. [Cancer Treat Rep 70:1451-1453, 1986].

5-Aza-2′-deoxycytidine (Aza-dC) is an antitumoral agent effective against murine (1) and human (2) leukemias. 5-Azacitidine is incorporated into both DNA and RNA, whereas Aza-dC is incorporated only into DNA (3-5). This difference may be at the basis of the recently reported higher activity of Aza-dC in inhibiting the growth of L1210 leukemic cells both in vitro and in vivo (6). Aza-dC, when incorporated into DNA, does not affect DNA synthesis but it inhibits DNA cytosine-methyltransferase, thus causing hypomethylation of the newly synthesized DNA (5,7,8).

The inhibition of DNA methylation by 5-azacitidine or Aza-dC has been proposed to explain these drugs' ability to cause differentiation (7,8), activating latent cellular genes (8). Although the molecular basis for the antileukemic activity of 5-azacitidine or Aza-dC is still unclear, it has been tentatively correlated to their ability to inhibit DNA methylation (6,9). Another possibility is that Aza-dC, when incorporated into DNA, alters DNA integrity. This hypothesis is supported by the recent observation that alkali-labile sites are present in L1210 cell DNA synthesized during drug exposure (10).

For either the inhibition of DNA methylation or the production of DNA alkali-labile sites, Aza-dC must be incorporated into DNA. Therefore, if DNA synthesis is inhibited (eg, by concomitant use of other drugs), the effect of Aza-dC could be reduced. In this paper we report that in L1210 mouse leukemia cytarabine (Ara-C), an antileukemic drug which blocks DNA synthesis given concomitantly with Aza-dC, antagonized the in vivo antileukemic activity of Aza-dC.

MATERIALS AND METHODS

Animals and Tumors

Male $CD2F_1$ mice (20 ± 2 g) received ip transplants of L1210 leukemia cells (10^5 cells/mouse). L1210 mouse leukemia was maintained by weekly ip passages in DBA/2 mice; $CD2F_1$ mice were used in the experiments.

Drugs

Ara-C and Aza-dC were provided by the Drug Synthesis and Chemistry Branch, National Cancer Institute, Bethesda, MD. They were freshly prepared and dissolved in saline. Doses which were active without causing weight loss were selected in pilot experiments.

Statistical Analysis

The significance of differences between groups was assessed by two-way analysis of variance and Tukey's test (11).

RESULTS

Table 1 shows the antileukemic activity of Ara-C, Aza-dC, or the two combined given as single or repeated doses to L1210-bearing mice. Ara-C at a dose of 800 mg/kg ip given on Day 3 or Day 5 or at 400 mg/kg on Days 3, 6, and 9 after tumor transplant was moderately effective. Aza-dC at a dose of 100 mg/kg ip given on Day 3 or Day 5 or 50 mg/kg on Days 3, 6, and 9 after tumor transplant was very active. When Ara-C was

[1] Received Feb 18, 1986; revised Aug 6, 1986; accepted Aug 20, 1986.
[2] Supported in part by a generous contribution of the Italian Association for Cancer Research, Milan, Italy.

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TABLE 1.—Survival time*

	Treatment Day 3				Treatment Day 5				Treatment Days, 3, 6, and 9			
	Control	Ara-C	Aza-dC	Ara-C + Aza-dC	Control	Ara-C	Aza-dC	Ara-C + Aza-dC	Control	Ara-C	Aza-dC	Ara-C + Aza-dC
Mean survival time ± SE (days)	9.0 ± 0.5	11.0 ± 0.3	25.6 ± 1.9	14.2 ± 0.5	8.7 ± 0.4	11.1 ± 0.3	15.4 ± 1.2	11.8 ± 0.2	9.0 ± 0.5	14.7 ± 0.2	25.2 ± 1.8	18.9 ± 0.5
T/C%	—	122	267	156	—	138	188	150	—	167	311	211

* Each group consisted of 8–10 animals. 10^5 L1210 cells were injected ip to $CD2F_1$ mice. Drugs were injected ip on Day 3 or Day 5 or on Days 3, 6, and 9 after tumor implant. Ara-C and Aza-dC single doses were 800 and 100 mg/kg, respectively, alone or in combination. Repeated Ara-C and Aza-dC doses were 400 and 50 mg/kg, respectively. T/C% = median survival time of treated mice/median survival time of control × 100.

combined with Aza-dC the survival time was significantly lower than after Aza-dC alone ($P < 0.000001$ for treatment on Day 3 and $P < 0.00001$ for treatment on Day 5).

As can be seen in the right-hand column of table 1, Ara-C also antagonized the antileukemic effect of Aza-dC ($P < 0.000001$) when L1210-bearing mice were treated repeatedly on Days 3, 6, and 9.

DISCUSSION

On the basis of available information on the molecular pharmacology of Aza-dC (5–10),we predicted that simultaneous use of this drug with an inhibitor of DNA synthesis would reduce its antileukemic activity. As DNA synthesis inhibitor we chose Ara-C because (*a*) it rapidly and efficiently inhibits DNA elongation in L1210 (12,13), theoretically almost totally preventing Aza-dC incorporation into DNA, and (*b*) it is among the most widely used and effective drugs in human leukemia. It may therefore be useful to know whether combining it with other antileukemic drugs is advantageous or not.

The present study shows that Ara-C given simultaneously with Aza-dC strongly reduces its activity against L1210 leukemia, probably because it prevents its incorporation into DNA. This suggests that, as already observed for the in vitro and in vivo leukemia, Aza-dC has to be incorporated into DNA.

Caution thus appears necessary in combining Ara-C with Aza-dC in the therapy of human leukemias, unless appropriate intervals are planned between the administration of the two drugs.

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Vindesine for Recurrent and Metastatic Cancer of the Uterine Cervix: A Phase II Study[1]

Walter U. Rhomberg[2,*]

Twenty-four patients with recurrent or metastatic cervical cancer were treated with vindesine (VDS) (2 mg/m²) on 2 subsequent days per week. Twenty patients were evaluable for response. There were six partial responses (30%) and no complete responses. The median remission duration was 6.5 months. The results indicate that VDS is active in the treatment of cervical cancer. Dose-limiting toxic effects were leukopenia and peripheral neuropathy. VDS should be considered in the treatment planning of combination chemotherapy for cervical cancer. [Cancer Treat Rep 70:1455-1457, 1986]

Chemotherapy for cervical cancer has gained interest during the last few years, since a variety of cytotoxic agents have been shown to be active in metastatic and locally recurrent disease. This is a report on a single-agent study with vindesine (VDS), a semisynthetic vinca alkaloid.

PATIENTS AND METHODS

This study was performed between 1980 and 1985 at the Department of Radio-Oncology of the General Hospital in Feldkirch. Twenty-four unselected patients with measurable or evaluable disease were entered in the study. Patient characteristics are shown in table 1 and the sites of metastatic deposits are shown in table 2. The initial stages of the disease were IA to IIB in nine patients and IIIB to IV in 15 patients. None of the patients had received prior chemotherapy, 17 had received prior radiation therapy for pelvic disease, and eight had had previous surgery.

VDS was given at a dose of 2 mg/m² on 2 subsequent days by iv injection. This cycle was repeated every week until disease progression or severe neurotoxicity occurred. The dose was modified according to wbc and platelet counts. This schedule was chosen because the serum and tissue curves of the VDS concentration suggested that twice-a-week doses might be superior to once-a-week doses (1).

Since 1982, a selected group of six patients were continuously treated with VDS, even when progression of the disease was documented. This procedure is part of a pilot study concerning a possible antimetastatic effect of VDS. The drug is a microtubule inhibitor which has shown anti-invasive and antimetastatic activity (2,3).

In the majority of cases the treatment was given on an outpatient basis. To be eligible for evaluation of response the patients had to have received at least three cycles or a total dose of 12 mg/m² of VDS. All patients but two received no further chemotherapy in case of progressive disease.

RESULTS

Clinical Response

Four of 24 patients were not evaluable for response due to concurrent follow-up problems or radiation therapy for metastatic disease. A partial regression > 50% in the initial tumor volume was observed in six of 20 patients (30%) evaluable for response. Two additional minor remissions with 25%-50% decrease in tumor volume were noted. The disease remained unchanged in three patients for 3, 4, and 1.5 months, respectively; all other patients had progressive disease.

The sites of metastatic disease in responding patients included lung and pleura, lymph nodes, skin and lymph nodes, skin, or pleural plus hepatic lesions. Among the local recurrences there were two partial remissions. All

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TABLE 1.—Patient characteristics

Characteristic	No. of patients
Entered	24
Evaluable for response	20
Evaluable for toxicity	22
Median age in yrs (range): 43 (26–81)	
Histologic typing	
Squamous cell carcinoma	23
Adenocarcinoma	1
Sites of disease	
Local recurrence only	9
Distant recurrence only	11
Local + distant recurrence	4
Karnofsky performance status (range): 70 (20–90)	

TABLE 2.—Distribution of distant metastases*

Site	No. of sites
Regional and distant lymph nodes	9
Lung	7
Skeletal system	6
Liver	5
Peritoneal cavity	5
Pleural cavity	5
Skin	3
Urethra	1
Bronchus	1

*Detection of metastases by clinical means at the beginning of treatment.

responding lesions but one were measurable. One local recurrence judged as partial remission was evaluable by means of palpation.

The median duration of partial response was 6.5 months. The median survival from the start of therapy with VDS was 7.0 months (range, 2.5–40) for the 20 evaluable patients. Five of these 20 patients lived > 1 year despite the limited duration of response. This was probably due to radiation therapy which was also given to some metastatic sites in six patients.

Toxicity

Twenty-two patients were evaluable for toxicity. In this series a median of 11 cycles of VDS was given per patient.

Leukopenia < 2000 cells/mm^3 was noted in six of 22 patients (27.3%); wbc counts between 2000 and 4000/mm^3 were seen in an additional six patients. Platelet count was affected in only one patient.

Peripheral neuropathy with paresthesias was seen in 14 patients and muscular weakness with loss of the deep tendon reflexes was seen in five patients. Progressive muscular weakness affecting predominantly proximal groups of muscles led to cessation of treatment three times. An ataxia related to position sense impairment has not been observed in this series. Neuropathies were sometimes pronounced at sites of pre-existing nerve damage. This observation was made previously (4) and confirmed in this study. For instance, if a tumor had damaged peripheral nerves or a chordotomy had been performed previously, the subsequent paresthesias in that area could be quite painful and clinically exceed the benefit of a remission. Neurotoxicity was reversible in all patients. The longest interval to full recovery from neurological symptoms was 3 months.

Reversible alopecia was noted in 12 patients (five severe), constipation with abdominal pain in five, fever 1 day after the bolus injection in three, nausea in two, and skin necrosis at the site of injection in two. Long-term administration of the drug led to weight gain and transient cramps of the lower extremities. There were no drug-related deaths.

DISCUSSION

Single-agent chemotherapy in cervical carcinoma was reviewed in 1977 by Wasserman and Carter (5) and in 1984 by Bowen (6). About 25 agents tested have shown a response rate of between 0% and 27%. Cisplatin has demonstrated response rates > 30% (7–9).

VDS has not been widely tested in cervical cancer so far. The results of this study identify a single-agent response rate for VDS which is as good as that for any single agent investigated to date. Some results suggest that VDS is cleared from the plasma chiefly by an extrarenal mechanism (10,11). Drugs whose activity and toxicity are not compromised by renal function are certainly needed, since urethral obstruction is a frequent finding in cervical cancer.

Cisplatin has similar single-agent activity and the combination of these two agents may warrant further investigation. The dose-limiting toxic effects are leukopenia and reversible peripheral neuropathy for VDS.

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Phase II Study of Cisplatin Therapy in Patients With Metastatic Carcinoid Tumor and the Malignant Carcinoid Syndrome[1,2]

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Chemotherapy experience in patients with metastatic carcinoid tumor has been limited by the infrequency with which such patients are encountered clinically. The only single agents which have consistently shown some degree of activity, albeit limited, are 5-fluorouracil and doxorubicin (1). There are, however, a number of single agents for which negligible experience has been recorded. Perhaps most prominent among these is cisplatin, a drug which has a broad range of activity encompassing a number of malignant diseases. The purpose of this study was to discern evidence of possible useful therapeutic activity of cisplatin given by rapid infusion in patients with metastatic carcinoid tumor and the malignant carcinoid syndrome.

All patients were required to be ambulatory, maintaining a reasonable state of nutrition, and to have histologically confirmed metastatic carcinoid tumor with elevated urinary 5-hydroxyindoleacetic acid (5HIAA) excretion. In addition, all patients had measurable areas of malignant disease to serve as objective indicators of response to therapy, usually defects on liver scan or malignant hepatomegaly. Patient characteristics and treatment regimen are shown in table 1. Patients were re-evaluated at 3 weeks and every 4 weeks thereafter. An objective response was declared if bidimensionally measurable lesions were decreased by at least 50% in the product of longest perpendicular diameters (30% in the sum of measurements for malignant hepatomegaly). A hormonal response was declared if the 24-hour excretion of 5HIAA was reduced by at least 50%.

Four patients were treated only at the 45-mg/m^2 dose because of early disease progression or because excessive toxicity precluded escalation. Eleven patients were either initiated at the 90-mg/m^2 dose (five patients) or escalated to this level at the second course (six).

Therapeutic response and toxicity data are shown in table 1. Among 15 patients in this study we observed only a single very transient partial objective and hormonal response that was not associated with symptomatic improvement. It was also discouraging that none of the remaining patients had even the slightest sugges-

TABLE 1.—Patient characteristics*,†

Characteristic	
Total	15
Male/female	11/4
Median age in yrs (range)	55 (34–70)
Performance score‡	
0–1	13
2	2
Prior chemotherapy	9
Median pretreatment 5HIAA in mg/24 hrs (range)§	168 (36–644)
Therapeutic response	
Objective tumor regression	1 (7%)
> 50% 5HIAA reduction	1 (7%)
Duration of regression (mos)	3
Symptomatic improvement	0
Median time to disease progression (days)	54
Toxicity	
Vomiting	8
Leukopenia (< 4000 to ≥ 2000 cells/mm^3)	6
Creatinine	
> 1.5 to ≤ 2.0 mg/100 ml	4
> 2.0 mg/100 ml	1
Neuropathy	1

*Unless otherwise specified, values = No. of patients.

†Cisplatin regimen was as follows: 90 mg/m^2 by 15-min iv infusion every 3 wks × 2, then every 4 wks. If severe syndrome, initial dose of 45 mg/m^2 escalating to 90 mg/m^2 if initial dose was well-tolerated. In addition, 3000 ml of iv hydration over 13 hrs + 12.5 g of mannitol and antiemetics were received.

‡Eastern Cooperative Oncology Group criteria.

§Normal to 6 mg/24 hrs.

[1] Received Mar 5, 1986; revised June 13, 1986; accepted July 16, 1986.

[2] Supported by Public Health Service grant CA-37224 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services.

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tion of objective or symptomatic improvement. In view of these considerations, we did not feel justified in extending this study, even though the 95% confidence interval for objective tumor regression would allow a maximum regression rate of 32%. We must conclude that there is no reasonable likelihood that cisplatin as a single agent, and by the methods we employed, is a treatment of substantial value for metastatic carcinoid tumor.

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"Role of Mathematical Modeling in Protocol Formulation in Cancer Chemotherapy"

I would like to comment on the article entitled "Role of Mathematical Modeling in Protocol Formulation in Cancer Chemotherapy" by A. J. Coldman and J. H. Goldie (1), which recently appeared in *Cancer Treatment Reports.*

Although the recommendations regarding chemotherapy protocols given in this paper may perhaps be correct, they do not follow the arguments advanced to support them. Moreover, those arguments seem to me to involve a number of incorrect hypotheses.

The article seeks to adapt the phenomenon of mutation to antibiotic resistance in micro-organisms to the apparently homologous development of resistance to antitumor agents in human neoplasms. That is, the argument is based entirely on somatic mutation in eukaryotic cells. From the sketchy arguments presented in the article, it appears that the underlying idea is the following. Since mutations conferring resistance to diverse agents are rare, independent events, the probability of resistant lines to all these agents is of a higher order than the individual probabilities. Thus, combination chemotherapy, at maximal permissible dosages, should be better than the individual agents given serially.

However, such an argument pertains only to the probability of a single cell mutating to resistance to all the agents involved. In fact, if the mutational events in question are truly uncorrelated, this argument merely implies that any population of (neoplastic) cells will contain independent subpopulations, each resistant to one of these agents. It cannot follow, from such arguments alone, whether combination chemotherapy is better or worse than sequential therapy. A closer mathematical analysis is called for, as is indicated below.

In addition, one of the authors' basic assumptions is simply not correct. Namely, they state [Assumption (b), p 1042]: "Sensitive tumor cells have a fixed probability per division of acquiring resistance to a particular drug *at a particular dose.*" In fact (assuming the agents themselves are not mutagenic), the entire thrust of mutation-selection mechanisms since Darwin's time implies that mutation rate must be *independent* of dose. This has some important implications. For instance, any apparent relation between dose and the appearance of resistance must itself be due to selection alone. For example, in the microbial systems the authors employ as a guide, it is well known that resistant cells are at a substantial disadvantage to normal (wild-type) cells in the absence of antibiotic. Hence, such resistant cells will normally be autonomously selected against, rapidly overgrown, and eliminated. At low antibiotic dosages, there will be a competition between selection mechanisms, whose outcome can only be predicted on the basis of more detailed models. The authors do not consider these facts at all. In any case, the issue involves population dynamics, and not intercellular mutational events.

Just to illustrate the kind of model necessary to investigate and justify the conclusions the authors draw, consider the following simplified situation. We have a population of size S(t) at time t of wild-type (sensitive) cells, a population of size $R_1(t)$ of cells resistant to agent α, and a population $R_2(t)$ of cells resistant to agent β. We want to write down the laws governing the sizes of these populations when (*a*) both agents are present simultaneously, and (*b*) the agents are given sequentially. The rate of change of each of these populations in time will generally depend on four kinds of processes: (i) inherent net reproductive rates; (ii) the effects of mutation; (iii) competitive interactions between populations; and (iv) the lethality of the agents. For the sake of illustration, we will neglect (ii) and (iii). Assuming exponential growth for all populations (note that we could equally well assume logistic growth or a more complicated growth law), and first-order kinetics for the interaction between cells and the chemical agents, we obtain a mathematically very simple general system of the form

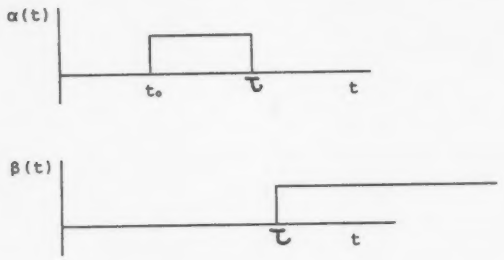
$$\frac{dS}{dt} = a_1 S - (\mu_1 \alpha(t) + \nu_1 \beta(t))S$$

$$\frac{dR_1}{dt} = a_2 R_1 - (\nu_2 \beta(t))R_1$$

$$\frac{dR_2}{dt} = a R_2 - (\mu_2 \alpha(t))R_2,$$

where the a's, μ's, and ν's are numerical parameters. These equations are independent of one another, since we assume no competition or mutation. The first term in each of them describes autonomous growth; the second term describes the effects of antitumor agents, whose concentrations $\alpha(t)$ and $\beta(t)$ are arbitrary environmentally controlled functions of time. To investigate the effects of *combination* therapy, we simply put these concentrations equal to fixed constants, and follow the en-

suing changes in population sizes with time. To investigate the effects of *sequential* therapy, we replace $\alpha(t)$ and $\beta(t)$ by step functions as indicated below:



The time τ is so chosen that, say, $R_2(\tau) = 1$ (ie, the subpopulation R_2, sensitive to the first agent α, has essentially disappeared). We then compare the two situations as a function of the parameter values involved.

Such investigations should be most helpful in evaluating both the importance of somatic mutation in drug resistance, and, if it is important, the therapeutic efficacy of different regimens and protocols. Clearly the kind of model sketched above can be adapted to any number of therapeutic agents, any kind of growth laws, and any kind of intercellular competition.

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June 27, 1986

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[2] I thank Dr. Ross Langley for valuable discussions.

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Reply

Dr. Rosen raises a number of concerns regarding a model for the resistance of tumor cells to chemotherapeutic agents. In general, the author has two major areas of criticism: the assumptions used in this modeling and the rigor with which the results were developed.

The author does not believe that the mutation rate is dependent on dose. Even a superficial examination of the literature on drug resistance shows tumors which are selected for resistance to methotrexate (for example) at one dose are not necessarily resistant to methotrexate at 100 times that dose. Literally hundreds of experiments have verified this. When defining resistance, we must make mention of both the drug and the dosage in question; otherwise, the state is not well defined. When dose dependence does not exist for a particular drug, the definition we employ is not incorrect; it is merely overly general. The competitive growth disadvantage of resistant bacteria is not universally true for resistant tumor cells. In cases where this occurs, low doses of drugs can produce competitive growth between the various types of cells, which is one of the reasons why we recommend giving high doses of drugs. After all, the object is to eliminate the tumor cells.

The author is correct in noting that the results are not deduced rigorously in our article. The article was constructed as an introduction for clinicians, as to how modeling may be used and in understanding the role of some biological parameters in explaining the effects of chemotherapeutic protocols. Articles have previously been published in *Cancer Treatment Reports*, and elsewhere, where a more detailed analysis is presented. The author may care to read these, especially reference 9.[1]

The author then proceeds to write down an illustrative model of this process in which mutation is ignored! Furthermore, he does not even bother to solve this "mathematically very simple general system." Thus, the assertion that somatic mutation theory alone cannot prove the results we contend is unsubstantiated. In order to select treatment strategies, it is necessary to examine measures of treatment outcomes (for example, mean numbers of remaining cells, probability of no tumor cells), place constraints on the system, and then select strategies which satisfy these constraints and optimize the outcome variable(s). We have used both the outcomes mentioned. If the author takes the time to write down equations which include mutation and a doubly resistant state (R_{12}, say) using these outcomes, then he will find that the conclusions contained in the paper are correct.

In conclusion, we reject the author's comments on the hypothesis that mutation rates are a function of dose since they are at variance with experimental results. Rigorous development of these results is already available in the literature using a more sophisticated model than he proposes. We agree that "such investigations" are "helpful in evaluating the importance of somatic mutation in drug resistance" and would welcome any significant contribution on this matter.

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August 13, 1986

[1] Coldman AJ, and Goldie JH. A model for the resistance of tumor cells to cancer chemotherapeutic agents. Math Biosci 65:291-307, 1983.

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Improvement in Cardiac Ectopy During Gamma Interferon Infusion: A Case Report[1]

Acute cardiac events are an infrequently studied area of drug toxicity with phase I therapy. While many drugs are known to have effects on cardiac rhythm and contractility, this is infrequently assessed extensively during early drug development. The interferons as a class have been associated with a variety of noteworthy cardiac events. We report here a case of a patient receiving gamma recombinant interferon during phase I testing who showed striking improvement in his cardiac ectopy with therapy.

CASE REPORT

A 64-year-old white male presented to Brooke Army Medical Center Oncology Service for evaluation and treatment of metastatic melanoma. He was asymptomatic and without any history of hypertension or other cardiac disease. His past medical history consisted of wide local excision of a Clark's level V melanoma in the midthoracic back in 1983. Multiple lymph node recurrences had been proven histologically within the left axilla, left inguinal region, and abdomen. He had never received prior chemotherapy or radiotherapy. His only medications at the time of cardiac evaluation and institution of therapy were acetaminophen and temazepam. He was fully ambulatory with a Karnofsky performance status of 80. Physical examination revealed a blood pressure of 132/78. His pulse was irregular with occasional extra beats. There was no jugular venous distention. Palpable adenopathy in the axilla and supraclavicular region bilaterally was felt to be due to metastatic disease. The lungs were clear to auscultation. The heart had an irregular rhythm with no murmurs, rubs, or gallops. There was no pretibial edema. Routine evaluations prior to therapy revealed normal liver function tests, normal electrolytes, and a normal cbc. A pretreatment ECG revealed a right bundle branch block with occasional premature ventricular contractions (PVCs). A chest x-ray was normal. A gated blood pool study was obtained, which revealed an ejection fraction of 46% and DV/DT of 1.40. Continuous Holter monitoring with a Marquette 8000 series monitor (Milwaukee, WI) was performed for 5 days prior to therapy and during the 5 days of recombinant DNA gamma interferon infusion. The study drug was administered by continuous infusion for 5 consecutive days (120 hours) in a dose of 0.1×10^6 U/m^2 daily. All results of monitoring were blinded to the investigators until completion of Course 1 of therapy. These results are shown in table 1. The patient had no symptoms throughout his course of therapy and was fully ambulatory during drug administration. One month after Course 1, monitoring was repeated for 48 hours prior to Course 2 and then daily for 5 days during the second course of treatment (*see* table 1). Again the patient was asymptomatic, and had normal serum electrolytes, normal cbc, and an unchanged ECG.

TABLE 1.—Holter monitoring results by day*

	Total PVC	Coupled PVC	Runs VT	Average heart rate (beats/min)	Maximum heart rate (beats/min)	SVE
Course 1						
Pretreatment						
Dec 4	22,451	79	7	96	130	3
Dec 5	18,989	71	1	96	130	15
Dec 6	16,785	31	4	93	128	22
Dec 7	15,502	53	8	93	128	8
Dec 8	18,199	45	3	92	125	1
Treatment						
Dec 9	9967	11	0	93	132	0
Dec 10	17,743	3	3	93	132	0
Dec 11	4594	1	1	105	134	5
Dec 12	774	0	0	105	134	0
Dec 13	1537	0	0	100	130	2
Dec 14	188	0	0	100	130	7
Course 2						
Pretreatment						
Jan 3	6700	2	0	92	120	8
Jan 4	3512	1	1	92	120	8
Treatment						
Jan 6	6603	2	1	98	132	5
Jan 7	2028	0	0	98	132	4
Jan 8	663	0	0	92	121	0
Jan 9	685	0	0	92	121	0
Jan 10	471	0	0	95	118	0
Jan 11	514	0	0	93	121	0

*VT = ventricular tachycardia; SVE = supraventricular ectopy.

DISCUSSION

We report a patient with extensive prior evidence of asymptomatic ventricular ectopy who showed a marked decline in the quality and quantity of ectopy during phase I recombinant DNA gamma interferon (Schering Corp) infusion. This decline was again observed with a second course of therapy. Interferons as a class have previously been reported to cause a variety of acute cardiovascular events (1). These have been described predominantly with alpha interferon preparations and include sinus tachycardia, atrial fibrillation (2), ventricular tachycardia (3), and myocardial infarction (4). Gamma interferon has also recently been reported in two patients to cause first-degree atrioventricular block which resolved (5). Decline of ventricular irritability seen in our patient manifested as a 100-fold decline in total PVCs and clearance of complex ventricular ectopy with the first course of therapy followed by a ten-fold decline in total PVCs and clearance of complex ventricular ectopy with the second course. Further monitoring of patients receiving gamma interferon will be required before attempting a comparison of alpha and gamma interferons in regard to cardiac toxicity. Possible etiologies to our observed occurrence remain speculative.

This patient is also representative of the difficulty in assessing acute cardiac toxicity in phase I antineoplastic drug testing. Had this patient been assessed only during his first or second day of either course of therapy, significant cardiac rhythm disturbances (World Health Organization Class IV) could have been attributed to this agent, when this in fact represented the patient's cardiac baseline. Alternatively, had this baseline ectopy been known despite his asymptomatic state, he might have been excluded as a candidate for phase I therapy. As with other ambulatory cardiac monitoring studies, the significance of ectopy encountered must be interpreted in light of ventricular function, making determination of ejection fraction a relevant prestudy parameter (6). Studies describing cardiac events without careful assessment of pretherapy parameters should be questioned as to whether events observed are truly associated with the administered therapy.

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July 23, 1986

[1] The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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High-Dose Carmustine and High-Dose Etoposide: A Treatment Regimen Resulting in Enhanced Hepatic Toxicity

The prognosis of patients with high-grade gliomas of the CNS remains bleak, with essentially all patients succumbing due to tumor. In an attempt to improve the response rate and survival, a phase I–II study was initiated with high-dose combination chemotherapy and autologous bone marrow transplantation (ABMT). Carmustine (BCNU) at a dose of 350 mg/m^2/day for 3 days (total dose, 1050 mg/m^2) followed by etoposide (VP-16-213) at a dose of 400–800 mg/m^2/day for 3 days (total dose, 1200–2400 mg/m^2) with ABMT 3 days later was planned. Individually, both agents had previously been evaluated for recurrent CNS tumors and had demonstrated antitumor activity (1,2). It was hoped that the combination would yield synergistic antitumor activity without overlapping nonhematopoietic toxicity, since the dose-limiting toxic effects of BCNU and VP-16-213 were pneumonitis and mucositis, respectively (3,4). Myelotoxicity was anticipated to be severe; therefore, ABMT was used to assure hematopoietic recovery. Hepatotoxicity of both agents had been previously described, although at higher doses than we had planned to administer (3,5). Since BCNU was felt to be the most active agent, it was administered at an essentially maximal dose. VP-16-213 was initially administered at a half-maximal dose (1200 mg/m^2), with the next escalation to maximal dose. Patients were eligible provided they had a recurrent primary CNS tumor by both clinical and roentgenographic criteria. Additionally, the patients could not

have had prior exposure to the proposed therapeutic agents and had to be suitable candidates for ABMT studies.

A total of four patients were treated, three at the first level and one at the next dose level. All patients had recurrent anaplastic astrocytoma with previous maximal radiation therapy without prior chemotherapy. Acute toxic effects of the treatment were generally mild. The median durations of neutropenia ($< 500/\mu l$) and thrombocytopenia ($< 20{,}000/\mu l$) were 10 days (range, 5–15) and 11.5 days (range, 0–16), respectively. One patient developed gram-negative sepsis and another developed a skin infection at a bone marrow aspiration site. All patients were able to be discharged from the hospital. None of the treated patients demonstrated substantial tumor response based on CNS tumor response criteria, although one patient neurologically improved without change in the computerized tomographic (CT) scan and another had an improved CT scan with worsening of neurologic status.

Although acute toxicity was generally tolerable, three patients developed evidence of hepatotoxicity 1–2 months after initiation of treatment. Two patients had a progressive fatal clinical syndrome characterized by ascites, hyperbilirubinemia, and thrombocytopenia. The third patient had transient ascites without liver function test abnormalities except for an elevated LDH. Pathological hepatic evaluation was not obtained for any patient. Three patients have died within 3 months of treatment, one from progressive neurologic deterioration and two from hepatic dysfunction. One patient is alive at 12 months posttherapy.

For almost all tumors, improved survival associated with chemotherapy occurs when active drugs are administered in combinations resulting in synergistic antineoplastic activity with subadditive overall toxicity. We therefore combined high-dose BCNU and high-dose VP-16-213 with ABMT to investigate the treatment of recurrent primary CNS tumors. Previously, both agents had demonstrated activity against those tumors. We had anticipated severe myelosuppression without overlapping nonhematopoietic toxicity. In the four patients that we treated, there was evidence of enhanced hepatotoxicity. Two patients developed unequivocal hepatic dysfunction characterized by hyperbilirubinemia, ascites, and severe thrombocytopenia within 1–2 months of treatment, which led to their death. Another patient developed transient ascites with mild liver function abnormalities. Although hepatotoxicity had been described with both agents, toxicity generally occurred at much higher doses. Severe hepatotoxicity with VP-16-213 has been observed only with cumulative doses > 5000 mg/m^2. In the largest phase I study, BCNU hepatotoxicity was observed at doses of > 1200 mg/m^2, although patients with malignancies of the CNS were more likely to manifest that toxicity. For patients with CNS tumors and BCNU doses < 1500 mg/m^2, the estimated frequency was 12.5%. In our limited series, two patients developed severe hepatic toxicity, and another had evidence of reversible toxicity. Although the number of patients that we treated was limited, it appears that this high-dose combination will be associated with an unacceptable level of severe hepatic toxicity. Without pathological material, the exact description of the toxicity remains speculative. BCNU has been associated with both hepatocellular necrosis and veno-occlusive disease.

In summary, in an attempt to improve the treatment for patients with primary tumors of the CNS, we initiated a high-dose phase I–II study with combination chemotherapy. Unfortunately, it appears that the combination of BCNU and VP-16-213 will be associated with an unacceptable frequency of severe hepatic toxicity without substantial tumor response. Our limited study demonstrates synergism towards toxicity without augmented antineoplastic activity. High-dose chemotherapy may yet have a role for refractory CNS neoplasms, provided that combinations not resulting in substantial extra-medullary toxicity be developed.

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July 28, 1986

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"Cisplatin Plus Etoposide as Second-Line Treatment in Advanced Ovarian Carcinoma"

Although I appreciate that De Lena et al (1) quoted the abstract by Piver et al (2) regarding the results of salvage therapy in ovarian adenocarcinoma, I would like to make three observations. (*a*) Our results of the effectiveness of weekly cisplatin as third-line chemotherapy in ovarian cancer have been published (3). (*b*) An update of our abstract of cisplatin plus etoposide has been accepted for publication (4). Of 25 patients with recurrent ovarian carcinoma in relapse following cisplatin alone or in combination, only two (8%) achieved partial response, 18 had stable disease, and five had progressive disease, thus demonstrating very minimal activity of this combination. (*c*) Although the authors claim that they have demonstrated that cisplatin plus etoposide is active as second-line treatment in advanced ovarian cancer, what they have reported is that of 25 patients not previously treated with cisplatin (only one had received prior cisplatin), one (4%) achieved a complete remission and nine (36%) achieved partial remission. This is not different from the seminal report of Wiltshaw and Kroner (5) a decade ago, in which they achieved a 26.5% partial remission rate in 34 patients relapsing after previous noncisplatin cytotoxic chemotherapy. What De Lena et al have demonstrated is that cisplatin is less effective in both overall response and percentage of complete remission as second-line therapy as compared to primary cisplatin therapy, and that the value of adding etoposide to cisplatin remains enigmatic.

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August 3, 1986

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ANNOUNCEMENTS

Oncology Practice 1987: A Perspective

Snowmass, Colorado, February 1-7, 1987

For further information, contact: Stephen E. Jones, MD, Sammons Cancer Center #4800, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246.

Fourth National Medical Reunion of the Instituto Nacional de Cancerologia of Mexico

Mexico City, Mexico, February 11-14, 1987

For further information, contact: Jaime G. de la Garza, MD, Continuing Medical Education, Instituto Nacional de Cancerologia-Mexico, Ave San Fernando, No. 22 Tlalpan, 1400 Mexico City, Mexico (telephone: 901-655-3217).

10th International Symposium of the Ludwig Boltzmann Research-Institute for Infections and Tumors of the Urinary Tract

Vienna, Austria, February 19-21, 1987

For further information, contact: Secretariat of the 10th International Symposium, c/o Vienna Academy of Postgraduate Medical Education, Alser Strasse 4, A-1090 Vienna, Austria (telephone: 0222-42-71-65).

35th Annual Meeting of the Radiation Research Society

Atlanta, Georgia, February 22-26, 1987

For further information, contact: Radiation Research Society, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3153).

An Update on the Recent Advances in the Diagnosis and Treatment of Lung Cancer

Columbus, Ohio, March 6, 1987

For further information, contact: Angie Leonard, Office of the Director of Clinical Oncology, Riverside Methodist Hospital, Columbus, OH (telephone: 614-261-4475).

American Radium Society Sixty-Ninth Annual Meeting

London, England, April 6-10, 1987

For further information, contact: Ms. Suzanne Bohn, Executive Secretary, American Radium Society, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3179).

Prediction of Tumor Treatment Response

Banff, Alberta, Canada, April 21-24, 1987

For further information, contact: Meg Keiser, Conference Secretary, American College of Radiology, 925 Chestnut St, Philadelphia, PA 19107 (telephone: 215-574-3153).

International Conference on Reproduction and Human Cancer

Bethesda, Maryland, May 11–13, 1987

For further information, contact: Drs. John J. Mulvihill (Landow Bldg, Rm 8C41) or Richard J. Sherins (Bldg 10, Rm 10N234), National Institutes of Health, Bethesda, MD 20892; or call Conference Manager, Ms. Mary E. Clark (telephone: 301-589-6760).

Critical Issues in Tumor Microcirculation, Angiogenesis and Metastasis

Pittsburgh, Pennsylvania, June 8–12, 1987

For further information, contact: R. Hilda Diamond, Associate Director, Biomedical Engineering Program, Carnegie Mellon University, Pittsburgh, PA 15213-3890 (telephone: 412-268-2521).

Second International Head and Neck Oncology Research Conference

Arlington, Virginia, September 10–12, 1987

For further information, contact: Gregory T. Wolf, MD, Veterans Administration Medical Center, Clinical Studies Office (153), 2215 Fuller Rd, Ann Arbor, MI 48105 (telephone: 313-769-7100, ext 755).

Second International Congress on Neo-Adjuvant Chemotherapy

Paris, France, February 4–6, 1988

For further information, contact: S.O.M.P.S., Hôpital de la Salpétrière, 47 boulevard de l'Hôpital, 75651 Paris Cédex 13, France.

Third International Conference on Adjuvant Therapy of Breast Cancer

St. Gallen, Switzerland, March 3–5, 1988

For further information, contact: Secretariat Prof. H. J. Senn, MD, Department of Medicine C, Oncology Center, Kantonsspital, CH-9007 St. Gallen, Switzerland (telephone: 719-219-KSSG CH).

PRE-PUBLICATION NOTICE FROM THE NATIONAL CANCER INSTITUTE
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